PRESENTED BY
DR. A. C. WARTHIN.

VOLUME 1 JANUARY, 1928 NUMBER 7

Hospital Library

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

CONTENTS

PAGE

Regeneration of Tubular Epithelium in the Human Kidney Following Injury by Mercuric Chloride. WARREN C. HUNTER 463

A Study of Twenty-two Thousand Eight Hundred and Eight Blood Sugar Estimations—Fasting and Postprandial—in Non-Diabetic Individuals. HENRY J. JOHN 470

Tuberculosis of the Gall Bladder. JAMES T. CASE 482

O-iodoxybenzoic Acid in the Treatment of Infectious Arthritis; Report of Eighty Additional Cases. JOHN B. YOUMANS 494

The Histopathology of the Tonsil in Acute Rheumatic Fever and Chorea. W. W. G. MACLACHLAN AND DE WAYNE G. RICHEY 506

Uncomplicated Exudative Synovitis. E. C. ROBICHAUX 513

Editorials 517

Abstracts 521

Reviews 525

College News Notes 529

Issued Monthly

ANN ARBOR, MICHIGAN

PROPERTY OF THE
PATHOLOGY DEPARTMENT.

PROPERTY OF THE
PATHOLOGY DEPARTMENT.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

EDITORIAL COUNCIL

ADDISON, JAMES R., ... Denver, Colorado
BARKER, L. F., ... Baltimore, Maryland
BOLDUAN, HARLOW, ... New York, N. Y.
BROWN, J. H., ... Toronto, Canada
CLEVELAND, G. B., ... Rochester, Minn.
EDDINGTON, C. G., ... Detroit, Michigan
LUCIETTI, JOHN A., ... Clifton Springs, N. Y.
MARTIN, CHARLES F., ... Montreal, Canada
MEISSEN, JOHN H., JR., ... New Orleans, La.
PERLSTEIN, JOHN, ... Cleveland, Ohio
SMITHIES, FRANK, ... Chicago, Ill.
STRONG, ALFRED, ... Philadelphia, Pa.
WARD, WILLARD J., ... Pasadena, California
WELLER, CARL VERNON, ... Ann Arbor, Michigan

DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

Editor

ALFRED SCOTT WARTHIN, M.D.
Pathological Laboratory, University of Michigan
Ann Arbor, Michigan

Price per volume, net, postpaid, $7.00, United States, Canada, Mexico, Cuba, $7.50 other countries

Copyrighted by The American College of Physicians

Entered as second class matter at the Post Office, Ann Arbor, Michigan

Regeneration of Tubular Epithelium in the Human Kidney Following Injury by Mercuric Chloride

By Warren C. Hunter, M.A., M.D.*

IT IS rather generally believed that the functional epithelium of the human kidney has only a limited regenerative capacity and that the clinical importance of this is negligible. The matter receives little or no consideration in most systems and textbooks of medicine and pathology. Yet in the voluminous literature on renal diseases are many descriptions of regeneration in the kidney of man and experimental animals, particularly after injury by the salts of heavy metals.

As long ago as 1879 Weigert (1) noted regeneration in the renal parenchyma of animals poisoned with chromic acid. Likewise Thorel (2) (1903) found marked evidence of regeneration in the kidneys of experimental animals within eight days after the administration of chromic acid. Heineke (3) (1909) in a study of a series of human cases in which death occurred from a few hours to several weeks after taking sublimate, noted that extensive cellular regeneration had taken place in the affected tubules. A remarkable experimental study of tubular cell regeneration is that of Oliver (4) (1915) who showed that in animals given a single injection of uranium nitrate there is regenerative activity in the epithelium of the damaged tubules as early as the fourth or fifth day after the injury and that the process continues until the tubules are completely relined by new cells. In a recent study of the pathology of the sublimate kidney in man Nakata (5) (1922) has also described the formation of new cells in the affected tubules. The list might be greatly lengthened but the references cited are sufficient to show that the recognition of cellular regeneration in the kidney is neither new nor rare.

In view of the importance of the possibility of the growth of new epithelium to replace that lost in the course of renal disease in man, and because of the apparent lack of its recognition in the medical textbooks, the writer felt it might be of interest to record the observations made in a recent case illustrating the point.

The following clinical data were furnished by Dr. Earl Smith, clinician in charge:

*From the Department of Pathology, University of Oregon Medical School, Portland.

Case History

R. MacD., female, age 41. Single. Occupation—laboratory technician.

Past History

Well until ten years ago at which time she suffered a nervous breakdown. Since then has been nervous and at times despondent.

On August 20th 1926 she took by mouth two 7½ grain tablets of mercuric chloride. The stomach was promptly emptied, egg albumin was given and the patient subjected to repeated sweating. No apparent ill effects developed and she was discharged after thirteen days apparently fully recovered.

Present Illness

July 10th 1927, following a period of mental depression she again took bichloride. The exact amount was unknown but the patient stated that she had swallowed a "handful" of tablets. (1.82 grains each). She was not found until about two hours after taking the poison. The stomach was then immediately pumped, following which egg white, magnesium sulphate and sodium bicarbonate were administered. There was considerable pain in the epigastrium, incessant vomiting of blood tinged fluid and profuse bowel movements. Within a few days there developed a marked mercurial stomatitis.

Following is a record of the daily urine output:

1st	day	anuria		
2d	"	"		
3d	"	"		
4th	"	5	ccs.	per catheter
5th	"	10	"	" "
6th	"	30	"	" "
7th	"	90	"	" "
8th	"	60	"	voided
9th	"	105	"	"
10th	"	270	"	"
11th	"	270	"	"
12th	"	135	"	"
13th	"	750	"	"

The urine was at all times alkaline in reaction and showed a four plus albumin content. At first no casts were present but later granular, epithelial and hyaline types appeared as well as leukocytes and erythrocytes in considerable numbers.

On the twelfth day there developed a severe diarrhea with frequent bloody stools having a foul odor. This persisted and increased in severity the last two days of life. There was also considerable hemorrhage from the lesions in the mouth. Toward the end the patient had frequent convulsions which could be controlled only by morphine and repeated inhalations of chloroform. Death occurred on the fourteenth day after taking the poison.

Autopsy (*Abridged*)

U. of O., Pathology No. 17,293.

The body is that of a small-statured fairly well nourished female 41 years of age. There is no evidence of injury or disease about the head or neck. The gums have been sutured by the embalmer and the oral cavity is accordingly not examined. The body is embalmed; body heat is absent; rigor mortis is present.

The colon and the greater part of the small bowel are distended and contain a dark bloody fluid. The mucosa in many places is diffusely reddish from hemorrhage but no foci of diphtheritic inflammation are found.

The kidneys are increased in size, each weighing 195 grams. The capsule strips readily exposing a smooth pale cortical surface. The surfaces made by sectioning reveal the cortex to be pale and swollen. The normal markings here are somewhat indistinct. There are no noteworthy gross changes in the medulla or pelvis.

The lungs are dark and boggy. On section there appears to be a moderate degree of passive hyperemia. About a number of the smaller bronchi are small patchy consolidations.

All other noteworthy pathological changes are listed in the pathologic diagnosis. Organs and tissues not mentioned are normal.

Microscopic

Kidneys: Most striking is the great reduction in the number of proximal convoluted tubules retaining the original epithelial lining. Instead most of these tubules are lined by cells differing widely from normal in both morphologic and staining characteristics. The cells are often flattened and elongated with nuclei poor in chromatin and exhibiting not infrequently beautiful premitotic and mitotic figures. In other tubules the cells may be quite irregularly shaped, at times columnar or even triangular. Occasionally tubules are found in which the young epithelial cells are projecting far into the lumen and there surrounding fragments or even necrotic cells, the cytoplasmic processes of the new cells pushing between the bits of debris and forming a network about the masses. Nearly everywhere the damaged tubules are almost fully relined by the types of cells above described. In addition to the abnormal morphology the regenerated epithelium is further distinguished from the original proximal convoluted tubular cells by the staining reaction of the cytoplasm. In hemotoxylin and eosin preparations this has a distinct bluish-pink appearance in contrast to the normal pinkish-red. This characteristic together with the abnormal shape makes it very easy to recognize the new cells.

No changes are detected in the epithelium of any of the tubules other than the proximal convoluted group. The glomeruli exhibit no noteworthy histological alteration. The interstitial tissue is everywhere edematous and in the medulla one sees fairly numerous collections of small lymphocytes. Beginning proliferation of the intertubular connective tissue is evidenced by the presence of mitoses in a few cells. Casts are not abundant in the tubules within the cortex but are fairly numerous in the larger collecting tubules in the medulla. The casts are mostly of the hyaline variety but some are made up of granular cellular debris with some admixture of erythrocytes. Calcification is not in evidence. (See Figs. 1, 2, 3, 4.)

Colon and Ileum:—Post-mortem necrosis of superficial epithelium; diffuse hemorrhage in the submucosa.

All noteworthy findings in the other organs are listed in the pathologic diagnosis.

Pathologic Diagnosis

Acute mercuric chloride nephritis with extensive regeneration of epithelium in the affected tubules;

Acute mercuric enterocolitis with hemorrhage;

Intra-alveolar pulmonary hemorrhage, passive hyperemia, edema, purulent bronchitis and early bronchopneumonia;

Chronic salpingitis, probably tuberculous;

Atrophy of uterus and ovaries;

Brown atrophy of myocardium and liver;

Parenchymatous degeneration of liver.

Comment

Microscopically the kidney shows evidence of a widespread injury to the proximal convoluted tubules which has been followed by cellular regeneration so extensive that the tubules are almost completely relined by a new and atypical cell differing very markedly from the original epithelium in size, shape and staining qualities. The degree of repair which has taken place within the short space of fourteen days is truly remarkable.

The case offers an excellent opportunity of comparing the process of regeneration with that which I have observed in the rabbit kidney. In an experimental study (6) it was found that regeneration of tubular epithelium begins almost constantly on the fourth to fifth day following the administration of sublimate. The new cells are derived largely by mitotic division of injured but still viable cells in those segments of the proximal convoluted tubules on which mercuric chloride acts

selectively and to a lesser extent from epithelium proximal and distal to the injured area. In the rabbit proliferation of cells, once it has begun, goes on very rapidly so that after twelve to fourteen days the tubules are fully lined by cells having exactly the appearance of those described in the human kidney under consideration. The new cells in the rabbit likewise show a tendency to push between necrotic masses in the lumina of the tubules. Heineke (loc. cit.) saw this in the human kidney and believed it to be a phagocytic phenomenon. It appears to me to be rather the result of retention of the loosely packed necrotic epithelium in the tubules until after the new cells have begun to grow. The appearance of phagocytosis of the debris is merely the result of the growth of the cell cytoplasm along the line of least resistance which often takes it into the spaces between the dead matter.

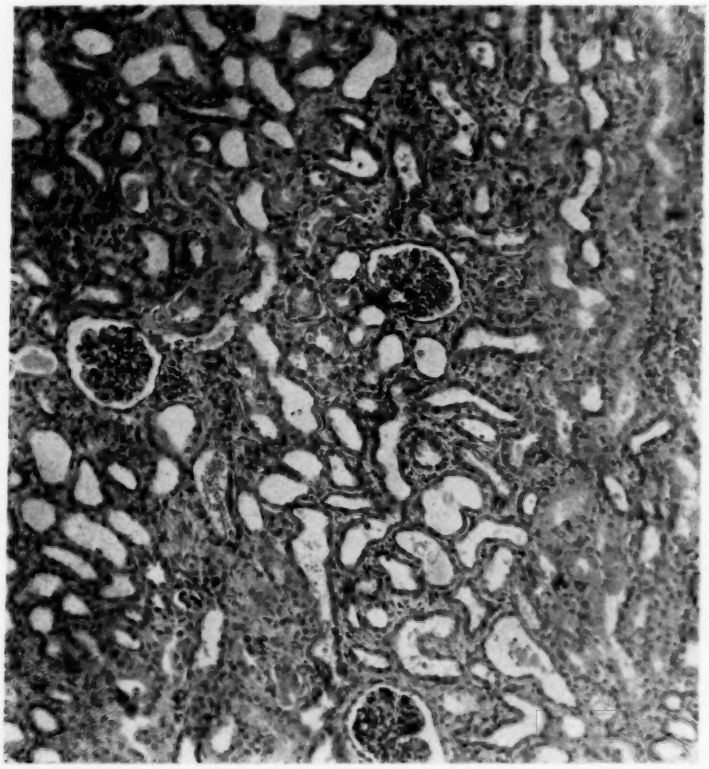


FIGURE 1.—Low power microphotograph of kidney cortex showing part of a labyrinth and medullary ray. Many segments of the proximal convoluted tubules are lined be regenerated epithelium. The small size and atypical flattened shape of these cells is the cause of the apparent dilatation of the affected tubules.

The regenerated cells have the staining reaction of embryonic epithelium. In the rabbit this persists over a period of several months and is very probably

permanent. To a lesser degree the abnormality in cell outline is found for a long time after completion of the reparative process. These features, together with the sharp localization of the injury to the proximal convoluted tubules, make it difficult to confuse the new epithelium with that of the descending limb of Henle to which it bears some resemblance.

Clinically the question as to functional ability of regenerated epithelium is of paramount interest. In the case at hand it would appear that the new cells were functioning. The combined urine output during the first six days was only 45 cubic centimeters. On the seventh day 90 cubic centimeters were obtained. From this time the urine excretion increased daily, reaching a total of 750 cubic centimeters on the day before death. The quantity of urine is of course in large measure dependent upon the condition of the glomeruli and although in microscopic sections these may exhibit no changes there may nevertheless have been severe functional injury with gradual recovery beginning at about the same time as the tubular repair. In any event it is seen that the kidneys were almost completely healed at the time of death and the urine output indicates increasing functional activity. It is quite

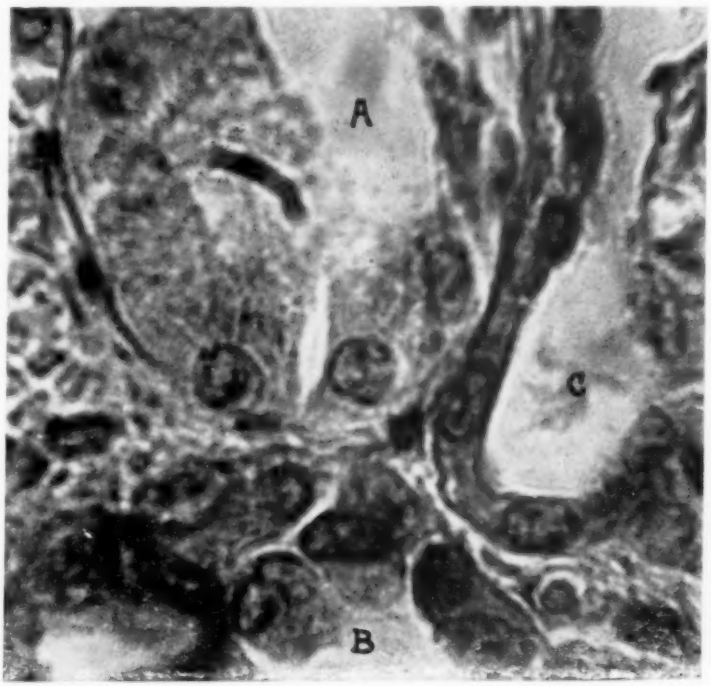


FIGURE 2.—High power microphotograph. (a) is a portion of proximal convoluted tubule in which the original epithelium has not been destroyed. At (b) and (c) the same tubule exhibits the type of cell characteristic of regenerated epithelium in this location. Note the striking contrast in the appearance of the two types of cells.

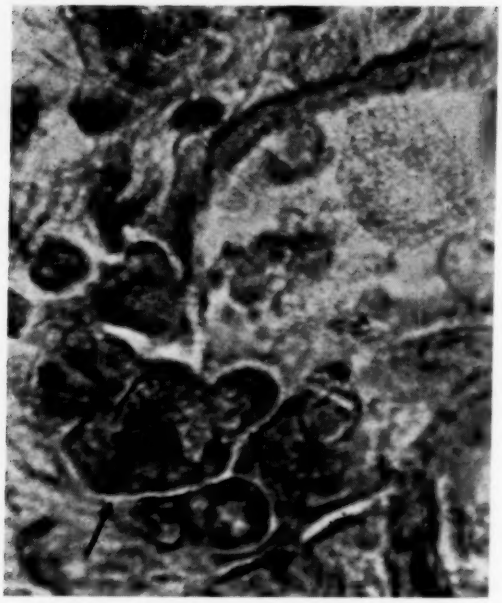


FIGURE 3.—Regeneration of renal tubular epithelium. The arrow points to a cell in mitotic division. The lumen of the tubule contains granular cellular debris. Near the mitotic figure are several newly formed epithelial cells. High power.

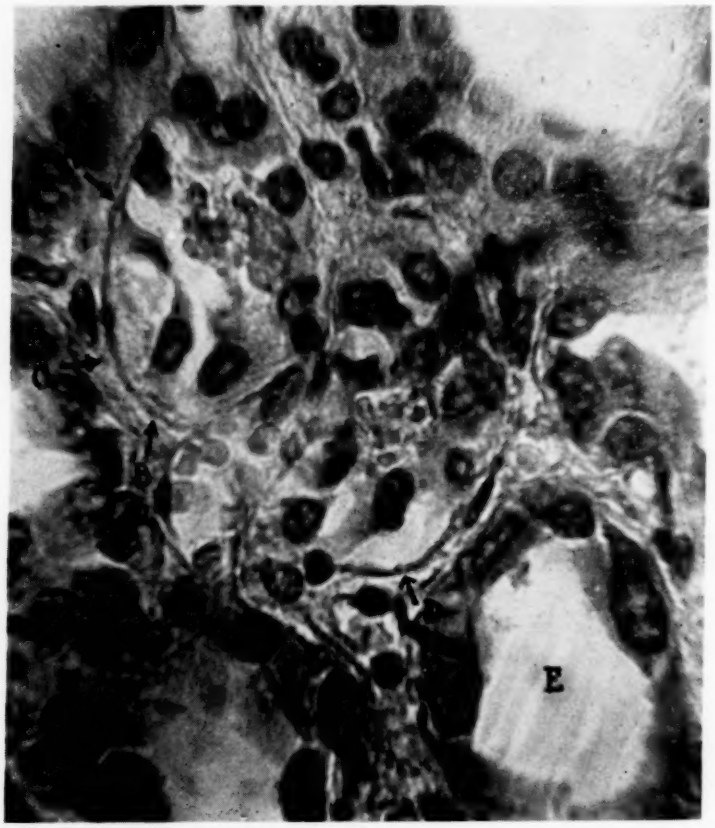


FIGURE 4.—High power photomicrograph illustrating the manner in which young epithelial cells (a) and (b) grow over and enclose necrotic cellular material. The same process is shown at (d). (e) is a tubule lined by typical regenerated epithelium.

possible that had not the intestinal lesions of mercury supervened the patient might have recovered. Whether or not secondary contraction of the kidney would have developed later is problematical. In rabbits repeatedly poisoned with small doses of sublimate such a change is in my experience almost uniformly present. It is possible that in the human kidney under consideration we are witnessing in the early proliferation of the stroma the first step in the direction of secondary contraction. Because of the lack of any urinary findings following the first poisoning a year before death it is impossible to say whether or not any of the regenerated epithelium dates from that time but the clinical course would indicate that there was no appreciable kidney damage.

SUMMARY

1. An instance of mercuric chloride poisoning in the human is presented in which the kidney exhibits almost complete regeneration of the tubular epithelium within fourteen days after injury.

2. The microscopic appearance of the kidney is strikingly similar to that observed in experimental animals at the same interval of time after sublimate poisoning.

3. The regenerated epithelium differs markedly from the normal in its histological and staining characteristics, thus facilitating easy and certain recognition.

4. Microscopic proof of healing and clinical evidence of increasing function indicate that the kidney was recovering from the effects of the poison.

5. Death was due in large measure to the intestinal lesions of mercury and terminal bronchopneumonia rather than to renal insufficiency.

REFERENCES

(1) WEIGERT, SAMUEL: VOLKMANN'S Klin. Vortr., 162-163. 1879. Cited by Heinecke, A., Beitr. z. path. Anat. 45: p. 107, 1909.

(2) THOREL, C.: Deutsch. Archiv. f. klin. Med. 77: p. 29, 1903.

(3) HEINEKE, A.: Beitr. z. path. Anat. 45: p. 107, 1909.

(4) OLIVER, JEAN: Journ. Exper. Med. 21: p. 425, 1915.

(5) NAKATA, T.: Beitr. z. path. Anat., 70: p. 282, 1922.

(6) HUNTER, WARREN C.: Acquired Immunity in Renal Epithelium. An Experimental Study, using Mercuric Chloride as a Nephrotoxic substance for Rabbits. To be published.

A Study of 22,808 Blood Sugar Estimations—Fasting and Postprandial—in Non-Diabetic Individuals

By Henry J. John, M.D., F.A.C.P., *Cleveland Clinic, Cleveland, Ohio*

A YEAR ago I analyzed the fasting blood sugar estimations in one thousand non-diabetic patients taken at random as they had presented themselves at the Clinic for various examinations. Previous to that time I had had the impression that with each advancing decade of life the fasting blood sugar rose within reasonable limits, so that, for example, in the sixth decade as much as 150 mg. of sugar per 100 c.c. of blood might be considered as a normal figure. My study of this series of 1000 cases disillusioned me in this respect, though in each decade there was a slight average rise in the fasting blood sugar, as is shown by the fact that it varied from 91.8 to 107.4. The average figures for the various decades are given in Table I.

The actual range of the fasting blood sugar in this group was from 60 to 189 mg. per 100 c.c., the few high figures appearing in patients afflicted with diseases of the kidneys.

The study here presented comprises an analysis of 22,808 blood sugar estimations including fasting blood sugar estimations and estimations made in the course of glucose tolerance tests. In each of these groups of tests there are, as one would expect, some variable factors which may have influenced the blood sugar content, such as the type and the caloric value of the last meal, the patient's mental condition, the effect of any disease which may have been present. None of these has been taken into consideration in this study, the purpose of which has been to present the findings in an unselected series of clinical cases as they have appeared for examination, with the exception that diabetic individuals have been excluded. To study the effect of each variable factor in each case would be almost an impossible task, and the result could not but be inaccurate, so that on the whole I feel that the present analysis will shed some light on existing conditions.

All the blood sugar analyses were made with oxalated blood, 10 mg. of potassium oxalate per 10 c.c. of blood; the actual estimations were made within a few minutes after the blood was taken and picrated, 1 c.c. of whole blood being used for the estimation, which was done by the Myer-Bailey method.

I was led to undertake the present analysis by the comparatively frequent finding of low blood sugar values—65

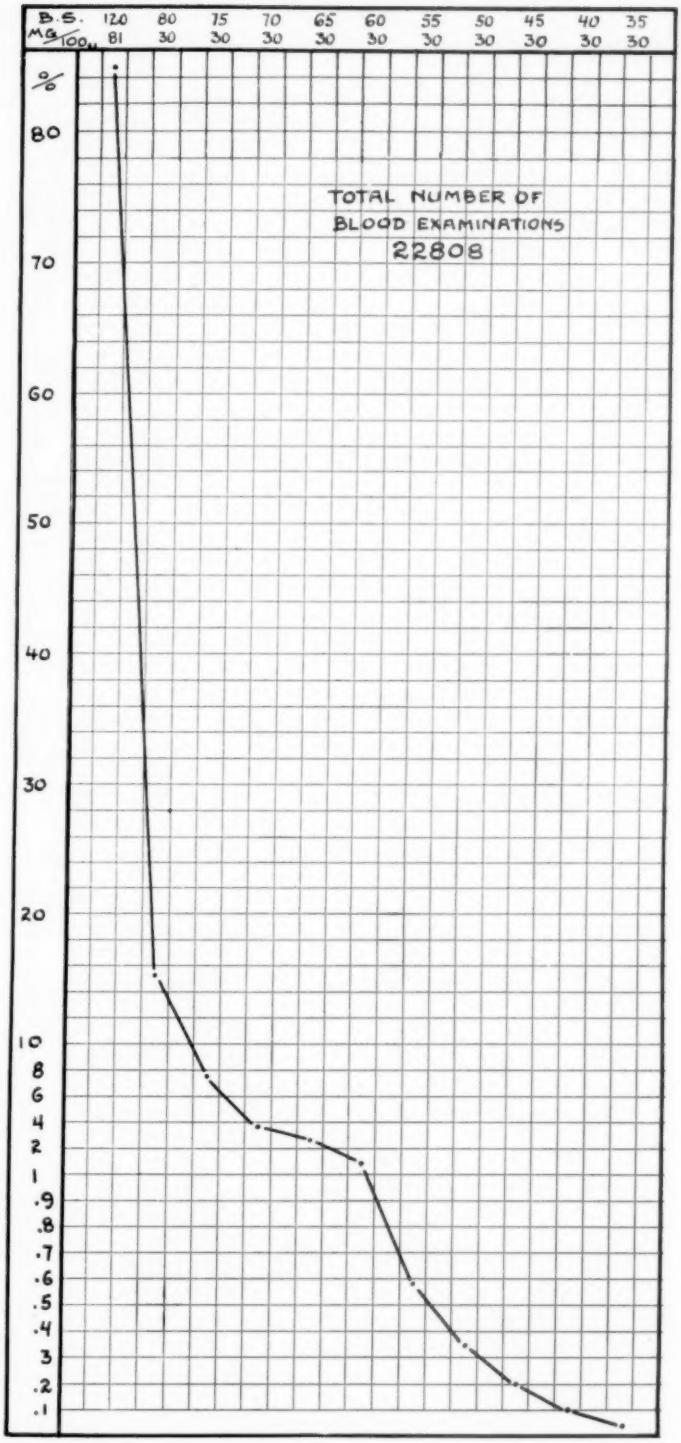

B.S. Mg/100 c.c.
120 81
80 30
75 30
70 30
65 30
60 30
55 30
50 30
45 30
40 30
35 30
%
80
70
60
50
40
30
20
10
8
6
4
2
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
TOTAL NUMBER OF
BLOOD EXAMINATIONS
22808

TABLE I

Average Fasting Blood Sugar Level in the Different Age Decades, As Shown by Blood Sugar Estimations in 1000 Non-Diabetic Individuals

Age Decade	I	II	III	IV	V	VI	VII	VIII
Aver. Bl. Sug. mg/100 c.c.	91.8	94.0	96.4	98.0	100.9	101.0	102.7	107.4

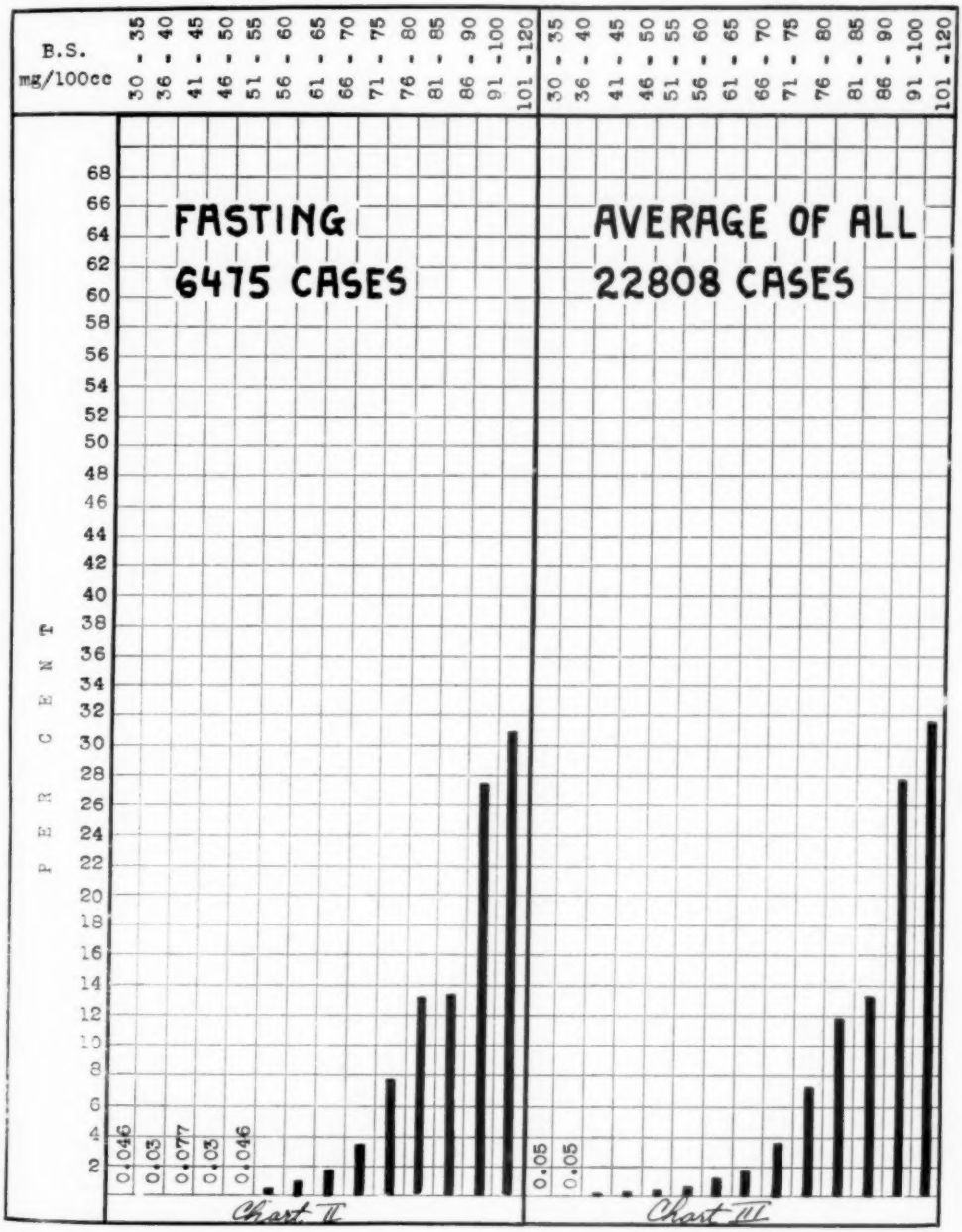
or fewer mg. per 100 c.c., in 494 cases of this series. I was anxious to see how often a low blood sugar content occurs in non-diabetic individuals; if possible, to see what might be the explanation of this low value; and to determine the relation of the low content to the ingestion of food. In an attempt to discover this last relationship the accompanying series of graphic charts (II-XV) was constructed.

In Table II are given figures in accordance with which these graphs were made. The figures for more than six hours after the ingestion of glucose could perhaps be considered as representing fasting blood sugar values, in which case the total number of fasting blood sugar estimations would be 7644 in place of 6475.

Table III shows the percentile relation between the total number of estimations (22,808) and the number of estimations in which the blood sugar was found to be below certain levels. These figures show clearly that the generally accepted idea that the range of normal non-diabetic blood sugar is from 80 to 180 mg. per 100 c.c.—depending upon the postprandial period—is incorrect; for in this series in 2452 estimations, or 15.14 per cent, the blood sugar was below this level. (See Chart I and III). Moreover, in the series of fasting blood sugar estimations (6475), in 954, or 14.73 per cent, the blood sugar values are 80 mg. per 100 c.c. or less, running as low as 30 mg. per 100 c.c. in these cases. (Chart II).

From glucose tolerance studies one finds that following the ingestion of 100 gm. glucose, in a non-diabetic individual there are two types of response—a moderate rise as high as 180 mg. per 100 c.c. in from one-half to one hour, with a return to the normal level at the end of one, one and one-half or two hours, or practically no rise whatever. In non-diabetic individuals one would expect to find a considerable rise at the end of the half hour and hour periods after the ingestion of glucose. However, I have not included in this report blood sugar values above 120 mg. per 100 c.c. for the reason that these higher values rarely appear on our records, as they have no diagnostic value whatever in the case of non-diabetic indivduals. These estimations were made only when the blood was taken to determine the presence or absence of some other metabolite, the blood sugar estimation being then made for scientific purposes only. However, Charts IV and V offer the interesting observation that during the first hour after the ingestion of glucose, in only 0.5 per cent of the cases the blood sugar value was 56 mg. per 100 c.c. or below.

In individuals who are strictly normal (as far as their insulogenic function is concerned) the blood sugar value one and one-half hours after the ingestion of glucose should be at the


B.S. mg/100cc
30 - 35
36 - 40
41 - 45
46 - 50
51 - 55
56 - 60
61 - 65
66 - 70
71 - 75
76 - 80
81 - 85
86 - 90
91 -100
101 -120
PER CENT
FASTING
6475 CASES
AVERAGE OF ALL
22808 CASES
0.046
0.03
0.077
0.03
0.046
0.05
0.05
Chart II
Chart III

normal level. The postprandial blood sugar curves usually show a more or less marked hypoglycemic "dip" after the primary postprandial rise, this being manifested chiefly at the end of the two and one-half and three and one-half hour periods, but, as can be noted from Chart VI, it appears during the earlier period in a considerable number of cases. This "postprandial hypoglycemic dip" I think can be explained as being probably due to the primary stimulation of the insulogenic apparatus by the ingested food, with a consequent heavy outpouring of insulin which, so to speak, burns up more than the normal amount of sugar so that the hypoglycemia is produced. In such cases the insulogenic apparatus may be considered to be hypersensitive, and this result has been described in the literature as "hyperinsulinism". This is the opinion of Depisch and Hasenöhrl.(2) Physical work brings about the same result, but, as I believe, in a different manner. Physical work results in a consumption of the muscle glycogen, which requires insulin. The secretion of the insulin once started continues as long as there is a demand for it, and if the liver is poorly stocked with glycogen, or if the demand for glycogen continues for too long a time so that the supply can not cope with

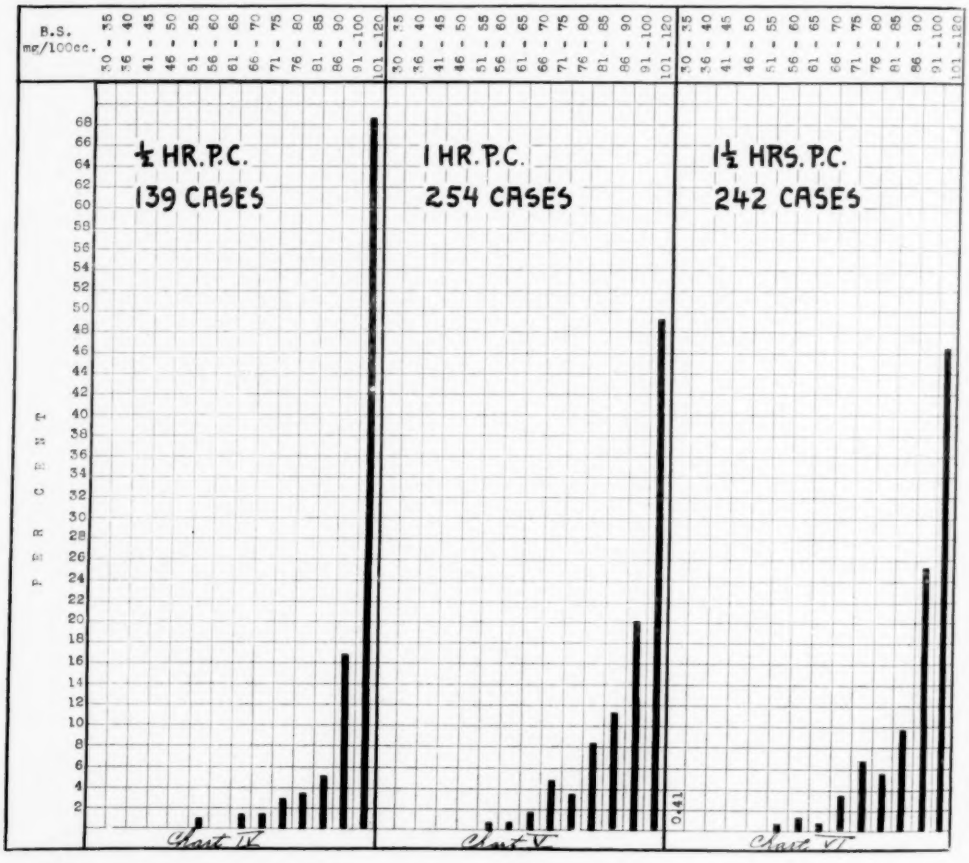


TABLE II

An Analysis of 22,808 Blood Sugar Estimations

(The figures represent the number of estimations in which the blood sugar was at the level indicated by the values given at the top of the columns.)

B. S. mg. pr. 100 c.c. Time	30 to 35	36 to 40	41 to 45	46 to 50	51 to 55	56 to 60	61 to 65	66 to 70	71 to 75	76 to 80	81 to 85	86 to 90	91 to 100	101 to 120	Total
Fasting	3	2	5	2	3	14	55	118	237	515	850	889	1784	1998	6475
½ hr. p. c.						1		2	2	4	5	7	23	95	139
1 hr. p. c.						1	1	5	12	9	21	29	51	125	254
1½ hr. p. c.	1					1	3	1	9	16	14	24	61	112	242
2 hrs. p. c.			1	3	6	6	17	15	31	54	97	95	203	381	910
2½ hrs. p.c.					1	4	3	12	26	53	105	120	281	392	997
3 hrs. p.c.	3	5	10	15	18	32	54	61	100	180	256	330	721	953	2738
3½ hrs. p.c.				2	1	1	10	23	59	112	176	234	472	621	1711
4 hrs. p.c.	4	4	7	9	18	33	58	80	143	220	357	391	859	860	3043
4½ hrs. p.c.				1	3	3	15	19	60	117	199	228	511	477	1633
5 hrs. p.c.				1	3	6	24	43	114	215	357	403	766	695	2627
6 hrs. p.c.					1		11	21	26	77	137	145	256	196	870
More than 6 hrs.					1	2	5	10	58	99	158	140	372	324	1169
Total	11	12	23	33	55	104	256	410	877	1671	2732	3035	6360	7229	22808

TABLE III

The Percentage Relation of the Different Blood Sugar Findings

	Total	Per Cent
Total number of blood sugar estimations	22808	100
Blood sugar from 81 to 120 mg. per 100 c.c.	19356	84.86
Blood sugar 80 mg. per 100 c.c. or less	3452	15.14
Blood sugar 75 mg. per 100 c.c. or less	1781	7.81
Blood sugar 70 mg. per 100 c.c. or less	904	3.96
Blood sugar 65 mg. per 100 c.c. or less	494	2.16
Blood sugar 60 mg. per 100 c.c. or less	238	1.04
Blood sugar 55 mg. per 100 c.c. or less	134	0.58
Blood sugar 50 mg. per 100 c.c. or less	79	0.34
Blood sugar 45 mg. per 100 c.c. or less	46	0.20
Blood sugar 40 mg. per 100 c.c. or less	23	0.10
Blood sugar 35 mg. per 100 c.c. or less	11	0.04

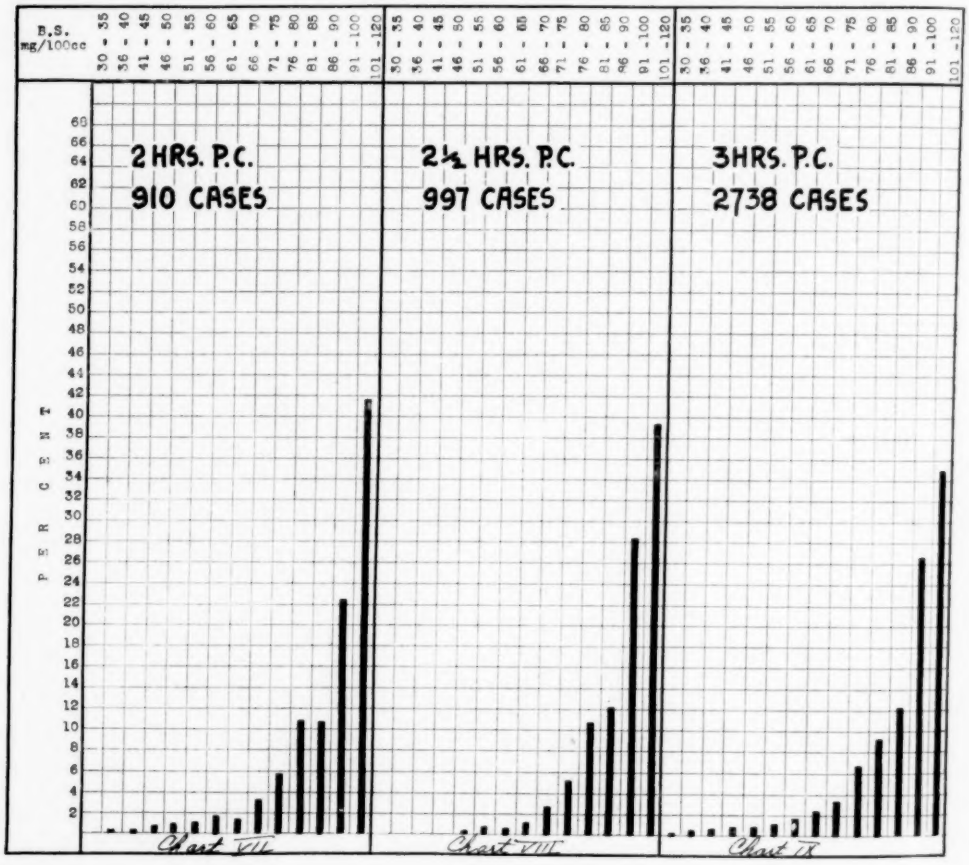
the demand, hypoglycemia is apt to occur.

The end of the second postprandial hour shows a definite increase in the number of low blood sugar values and a relative decrease in the higher values. (See Chart VII).

At the end of two and one-half and three hours after the ingestion of glucose this increase in the number of low values is even more marked. (See Charts VIII and IX). For years I have held the opinion that for the diagnosis of diabetes it is not the fasting blood sugar value that gives the requisite information, but rather the level of the blood sugar two and one-half or three hours after a fairly heavy carbohydrate meal. An estimation of blood sugar during this period helps

one to weed out the early diabetics from the non-diabetics, to distinguish between diabetic glycosuria and non-diabetic glycosuria. During this period—two and one-half to three hours after a meal, a normal individual will present a normal blood sugar no matter cut to a glucose tolerance curve and has an important clinical application in the differential diagnosis of diabetes.

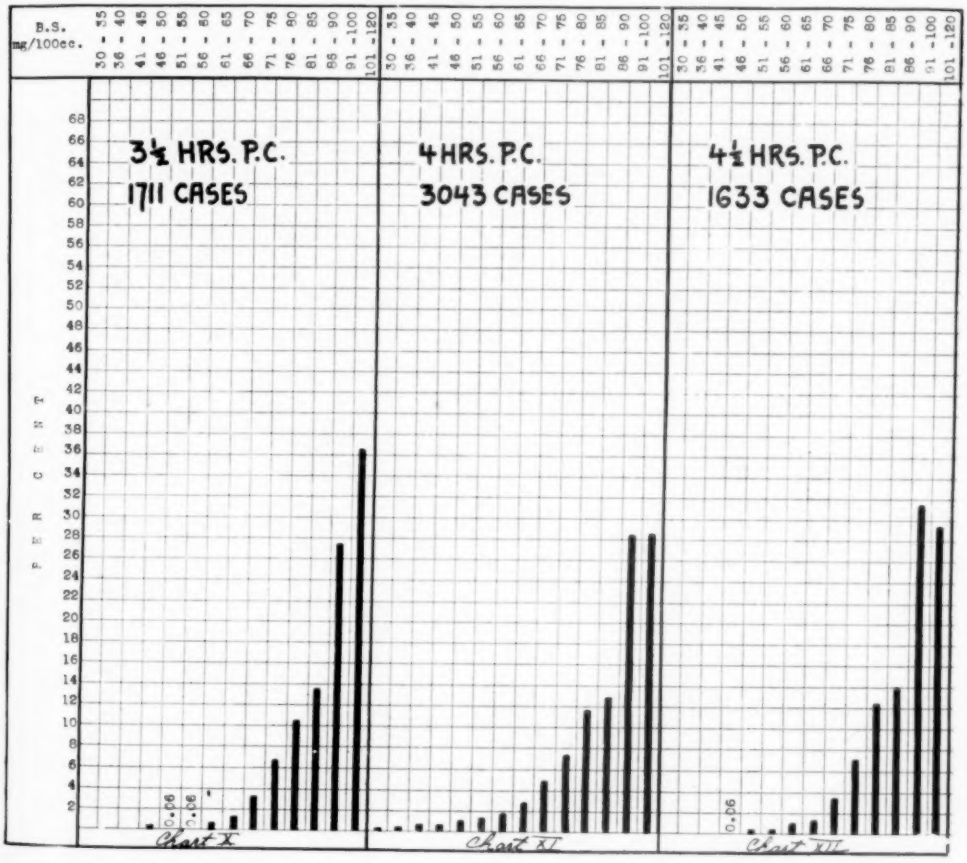
Charts X to XV represent respectively the blood sugar findings 3½, 4, 4½, 5, 6, and more than 6 hours after a meal. With the exception of the



what the carbohydrate content of the meal may have been, whereas a diabetic or a prediabetic individual can not present a normal blood sugar at this time, even though his fasting blood sugar may be within the normal limit. An estimation of the blood sugar two and one-half or three hours after a meal is therefore, so to speak, a short three and one-half and four hour periods, the blood sugar values for the most part lie between 70 and 120 mg. per 100 c.c., although the first two show quite a few low values, 5.26 per cent lying below 70 mg. per 100 c.c. These observations, which differ so widely from the generally accepted idea regarding the range of normal

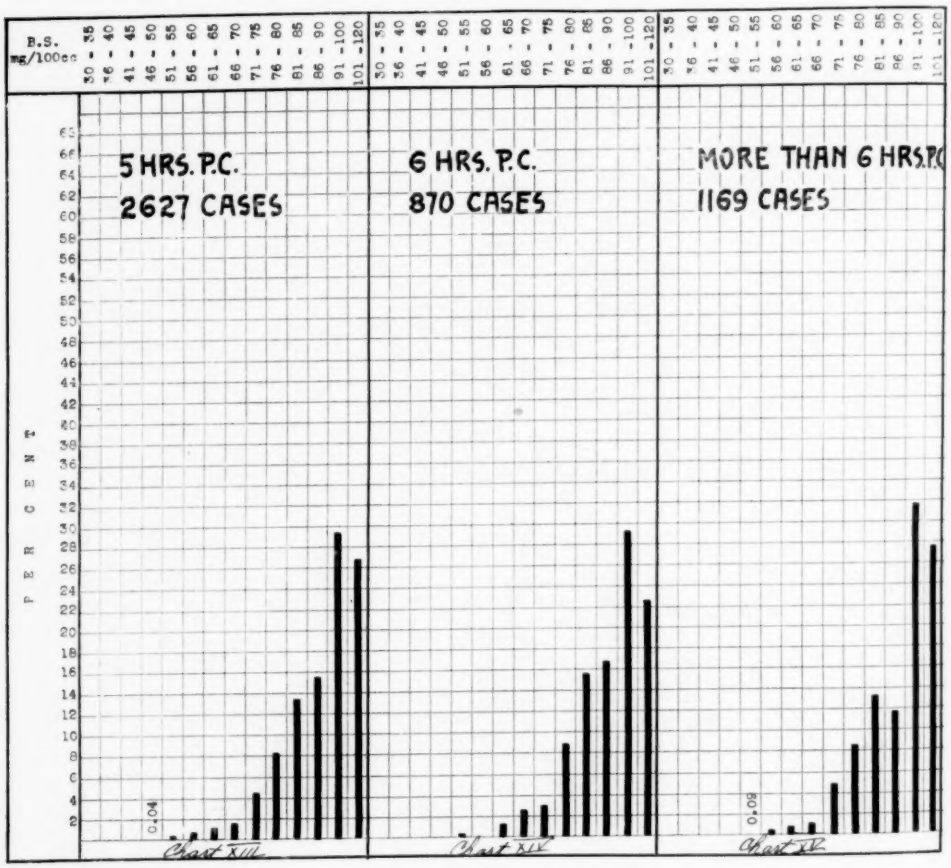
fasting and postprandial blood sugar, lead one to consider the mechanism for the initial sugar metabolism.

The blood sugar content is affected by two factors, one of which is exogenous, the other endogenous. The exogenous factor is food, the endogenous factor is the direct transformation of the glycogen in the liver into the glucose or sugar in the blood. All the tissues of the body play a large role in metabolism of the exogenous sugar; the liver is the one effective agent in the storage of glycogen and its transformation into glucose. Thus earlier postprandial estimations really give an indication of the exogenous regulation of the blood sugar. The exogenous regulation, on the other hand, is effective principally after more than six hours after the ingestion of food. Of this factor the "fasting" and the "more than six hours postprandial" blood sugar values are an indication.



There are two chief theories as to the mechanism which keeps the blood sugar within normal limits. First, there is the mechanistic theory which holds that the blood sugar content is maintained by a simple process of diffusion, which presupposes that a like

blood sugar level is maintained in both the liver and the blood. The second is the secretory theory which holds that the blood sugar level is maintained by the secretion by the liver of the necessary amount of glucose into the blood stream. Following a carbohydrate meal hyperglycemia ensues, which is quickly balanced by the absorption by the tissues of the excess of sugar from the blood. That this resorption is a vital process is indicated by the varying amounts of sugar in the different organs, the amounts at times even exceeding the concentration in the blood. One cannot explain the quick removal of the sugar from the blood stream as being due to its consumption and the formation of glycogen, since both of these processes are very slow in their action; and for the proper storage of glycogen insulin is necessary, as has been shown by Best and others.(3)



Perhaps the mechanism for the normal regulation of the blood sugar may best be understood by a study of its derangement which is affected by three factors: 1. the nervous system; 2. the liver; and 3. the insulogenic ap-

paratus. These factors may act directly or indirectly. The direct effects are those in which no definite regulating factor is totally destroyed but in which they are merely deranged (functional effects), so that their total harmonious cooperation is interfered with The indirect effects are then produced when one of the three regulating factors is destroyed. Thus a diseased condition of the liver will produce directly a derangement of the exogenous factor of the blood sugar regulation; while the extirpation of the liver or poisoning of the liver by phosphorous produces indirectly a derangement of both the exogenous and endogenous factors. On the other hand, stimulation of the sympathetic nervous system will produce hyperglycemia either directly or indirectly as the result of a decreased secretion of adrenalin, which produces the so-called adrenalin hyperglycemia.

Folin and Berglund (4) say that hypoglycemia is probably quite as normal a consequence of carbohydrate ingestion as hyperglycemia, but comes later. "Hypoglycemia is probably a reflection or index of a decreased need for sugar transportation from one set of tissues to another. This condition is obtained when there is an abundance of available carbohydrate material in all the tissues. A general abundance of other suitable food than glucose, notably fat (olive oil) may, therefore, also produce hypoglycemia. Hypoglycemia (in venous blood) can occur even during a prolonged moderate sugar absorption from the intestine, because the absorbed sugar may get by the liver but does not get into the venous blood."

The appearance of hypoglycemia in Marathon runners at the end of the race is a well known fact. Burger and Martens (5) extended similar observations to less strenuous exercises (running for one hour, fencing for 50 minutes, etc.). Two out of seven of the subjects became hypoglycemic, in one the blood sugar dropping from 90 to 61. My own observations do not include any strenuous exercise, outside of walking in a few cases.

The question of adrenalin hyperglycemia has been much discussed in the literature, but I shall quote only the experiments of Ulrich and Rypins (6). These authors administered ¼ c.c. of 1:1000 adrenalin (Parke Davis and Co.) subcutaneously and intravenously. Their results can be summarized as follows:

Average blood sugar, fasting
100 mg. per 100 c.c.
Adrenalin, ¼ c.c., 1:1000, injected
Blood sugar in 15 minutes
114.8 mg. per 100 c.c.
Blood sugar in 30 minutes
103.8 mg. per 100 c.c.
Blood sugar in 60 minutes
99.4 mg. per 100 c.c.

Ambard, Schmidt and Arnovlyevitch (7) have shown that the rate of oxidation of glucose depends on the concentration of insulin as well as of glucose in the blood. The glycemic level also influences oxidation indirectly by increasing the secretion of insulin.

Simon (8) reports a higher level of blood sugar in psoriasis, furunculosis, and eczema, especially in the chronic cases.

In discussing the disappearance of sugar from the blood stream, Cori and Cori (9) conclude from their experiments on animals that an excess of in-

sulin leads to an increased sugar oxidation. According to these authors glucose oxidation and glycogen formation accounted for 90 per cent of the sugar absorbed during four hours in both normal and insulinized animals.

Maranon (10) made glucose tolerance estimations in four cases of progressive muscular atrophy, using only 25 gm. of glucose. In every case the sugar metabolism exhibited a prediabetic lack of balance, the extent of the induced hyperglycemia paralleling that of the atrophic process.

The question as to whether vagus stimulation affects the production of insulin, bringing about a hypoglycemia, is discussed by Clark (11), who concludes that the stimulation of the vagus causes a secretion of insulin which in turn causes hypoglycemia.

Papilian and Jianu (12) produced hyperglycemia by severing both vagi in 10 dogs.

These few citations from the literature are offered merely to indicate the views of certain investigators as to the possible factors concerned in the production of hyper- and hypoglycemia.

Conclusion

An analysis of the 22,808 blood sugar estimations made from the blood of non-diabetic individuals is presented—the blood sugar in each instance has been analyzed as to its height in relation to the length of the postprandial period. The range for normal blood sugar as usually given is from 80 to 180 mg. per 100 c.c. but the present analysis shows that in 2452, or 15.14 per cent of these estimations, the blood sugar is 80 or below; and that in 1791, or 7.85 per cent, it was 75 mg. per 100 c.c. or below, the lowest value being 30 mg. per 100 c.c. Such a high percentage of blood sugar values below 80 mg. per 100 c.c. would indicate that these low blood sugar values are not of rare occurrence. Furthermore that they are apparently normal for these individuals is indicated by the fact that no special complaint is noted in the histories of the cases which I have especially investigated. We used to be alarmed when exogenous insulin lowered the blood sugar below 60 or 65 mg. per 100 c.c. but here is a definite demonstration that endogenous insulin apparently does the same thing, the patient not even being conscious of the low blood sugar content.

References

(1) John, H. J.: A study of fasting blood sugar and urea in non-diabetic patients, Ann. Clin. Med., 1926, 5: 340-352.

(2) Despisch, F. and Hasenohrl, R.: Beitrayg zur Blutzuckerregulation, Klin. Wchnschr., 1926, 5: 2001-2048.

(3) Best, C. H., Hoet, J. P. and Marks, H. P.: The fate of sugar disappearing under the action of insulin, Proc. Roy. Soc., 1926-27, s. B., c., 32-54.

(4) Folin, O. and Berglund, H.: Some new observations and interpretations with reference to transportation, retention and excretion of carbohydrates, J. Biol. Chem., 1922, 51: 213-273.

(5) Burger, G. C. E. and Martens, J. C.: Der Blutzuckergehalt bei Muskelarbeit, Klin. Wchnscher., 1924, 3: 1860.

(6) Ulrich, H. and Rypins, H.: A note on adrenalin hyperglycemia in man,

J. Pharm. & Exper. Therap., 1922, 19: 215-220.

(7) Ambard, L., Schmid, F. and Arnovlyevitch, M.: Application des lois d'action des diastases a la combustion du glucose chez le sujet sain et chez le diabetique, Presse med., 1924, 32: 721-723.

(8) Simon, F.: Blutzuckergehalt und Insulinbehandlung in Dermatosen, Arch. f. Verdauungskr., 1926, 37:363-370.

(9) Cori, C. F. and Cori, G. T.: Fate of sugar in animal body, J. Biol. Chem., 1926, 70:577-585.

(10) Maranon, G.: The blood sugar in muscular atrophy, Arch. de Endocrin. y. Nutricon, Madrid, 1926,

(11) Clark, G. A.: The influence of the vagus on the islets of Langerhans, J. Physiol., 1924-25, 59:466-471.

(12) Papilian, V. and Jianu, M., L'influence de la vagitomie double sur la glycemie, Compt. Rend. Soc. d. Biol., 1927, 96:70.

Tuberculosis of the Gall Bladder*

By James T. Case, *Battle Creek, Michigan*

TUBERCULOSIS of the gall-bladder is one of the rarest of pathological findings. The older text-books either make no mention of it at all, or ascribe to it a hypothetical great rarity without any reference to actually observed cases. Although tuberculosis of the liver and of the intrahepatic biliary passages is no great rarity, and although the researches of many writers (Fraenkel and Krause, Joest and Ernshoff, Rabinowitsch, Calmettee and Guerin, etc.) have shown the frequent presence of living tubercle bacilli in the bile of the gall-bladder in cases of tuberculosis, both with and without involvement of the liver, the relative great immunity of the mucosa of the gall-bladder to tuberculous lesions has been commented upon many times. The many French observers who were especially interested in tuberculosis of the liver and intrahepatic biliary lesions saw no tuberculous involvement of the gall-bladder in their cases. Veterinary observations confirm the same immunity of the gall-bladder to tuberculous lesions in cases of animal tuberculosis.

The last edition of Aschoff's Specielle pathologische Anatomie says that "tuberculosis of the gall-bladder is a rare finding. According to Simmonds two forms exist: A chronic form with thickening of the wall and chronic ulceration (chronic ulcerative tuberculous cholecystitis), and an acute form in which there are multiple small, bile-stained necroses in the mucosa containing tubercle-bacilli."

Simmonds in 1908 could find in the literature only four published observations on tuberculosis of the gall-bladder, the cases of Heddäus, Schmidt, Kisch and Beitzke.

Heddäus (1894) reported the first case of apparently primary tuberculous cholecystitis, in a married woman of the age of 44 years. For two years she had had violent coughing without expectoration; and for seven months had noticed a swelling in right side, which was not painful but hindered her work. This was opened by her physician and an abundance of pus was discharged. In three weeks the swelling had again appeared in the same place, painless and without other symptoms except sensitiveness on pressure. A fistula developed in the old incision and there was a continuous discharge of pus. On entering the Clinic, her examination showed moderate nutrition, moderate kyphoscoliosis, small goitre, normal lungs and heart, abdomen distended, soft, with many old striae, and separation of recti. In the right hypochondrium below the ribs there was a tumor mass measuring 10x15 cms. The skin was

*From the Surgical Clinic of the Battle Creek Sanitarium, Battle Creek, Michigan.

movable over this except at the site of the fistula in the mammary line at edge of ribs. The mass moved on respiration Percussion gave a dull tympanitic tone over it. Temperature on entrance 38.2°, later became normal. Urine negative. Clinical diagnosis of cholecystitis. Operation showed a subcutaneous cavity lined by granulation tissue, communicating by fistula with greatly enlarged gall-bladder. Two tablespoonfuls of caseous pus escaped from the latter on incision. Its cavity was curetted and packed. Microscopical examination of the curettings showed numerous caseous areas with giant-cells throughout the granulation tissue. When seen two years later patient seemed well and felt well save for persistent cough. Fistula had completely healed. Examination of lungs wholly negative.

Schmidt's (1896) case is quoted by Simmonds as being also one of chronic tuberculous ("caseous purulent") cholecystitis with cholelithiasis; but the details of this case are not given, and the reference is not accessible.

Kisch's (1902) case was that of a woman, of the age of 57 years, suffering from paranoia chronica and tabes, with optic atrophy of 13 years duration. Eight days before death she developed fever and pulmonary symptoms. There was no suspicion of gall-bladder disease. The clinical diagnosis was bilateral croupous pneumonia. Autopsy showed a chronic pulmonary tuberculosis, tuberculosis of the bronchial nodes, old tuberculous pericarditis, tuberculous ulcers in ileum, and chronic tubercles in liver, spleen and kidneys. The gall-bladder was adherent to neighboring structures and communicated by a small perforation with the colon. Its cavity was filled with gall-stones, 24 in number, about the size of peas, and with thick yellowish pus. The mucosa of the bladder was converted throughout into caseous masses, 4-5 mm. thick. Towards the serosa the caseous zone changed into a grayish translucent tissue; on the liver side the caseous masses invaded the liver in foci, many of which were as large as hazel-nuts. The distal fourth of the cystic duct showed the same appearances of caseation. In a distended portion of the duct there was a pea-sized stone. The hepatic and common ducts appeared normal, and contained apparently normal bile. No tuberculous lesions were found in the stomach, duodenum or jejunum. The microscopic examination of the gall-bladder wall showed a typical picture of tuberculous caseation, epithelioid tissue and giant-cells, with numerous tubercle bacilli in the lesions. No bacilli were found in the pus contained within the cavity of the gall-bladder. Kisch regarded the process as chronic and most probably the result of a haematogenous metastasis of tubercle-bacilli, excreted through the liver into the bile, and giving rise to the tuberculous infection of the gall-bladder mucosa as a result of its lessened resistance due to the gall-stones and the blocking of the cystic duct.

Beitzke's case (1905) was that of a 57 year old male, dying of tuberculous meningitis and general miliary tuberculosis. The autopsy showed in addition extensive caseation of left testis and epididymis, seminal vesicles and prostate, calcified bronchial and mesenteric nodes, old fibroid apical tubercu-

losis on the right, and scattered intestinal ulcers. The gall-bladder was of the size of a goose-egg; its external surface tense and shining like tendon; its cavity distended. On opening it was found full of a yellowish-green pus-like fluid. In the entrance into the cystic duct there was a hard pigment stone about the size of a cherry. The gall-bladder wall was several mm. thick, thickly beset with miliary gray to grayish-yellow nodules, giving it a shagreened appearance. Only in a few spots was the mucosa visible, but in such places it had lost its velvety appearance, and was either smooth or showed fine scar-like folds of a grayish color. There was no imbibition of bile. The microscopic examination showed that the mucosa was almost completely destroyed by the nodules and replaced by tuberculous granulation tissue which infiltrated the whole submucosa, and extended deep into the muscularis, interrupting it in places. The increased thickness of the wall was due chiefly to the thickening of the submucosa which constituted about two-thirds of the entire wall. It consisted of dense fibrous connective tissue without tubercles. The contents of the bladder were not pus, but consisted chiefly of amorphous mucoid masses with a few epithelial cells and leucocytes. Occasional tubercle-bacilli were found in smears made from it. Since tubercle bacilli have been found frequently in human bile without accompanying lesions of the gall bladder, Beitzke thinks that there must be some especial predisposing factor in the production of gall-bladder tuberculosis, and this he finds in the chronic cholecystitis and cholelithiasis. He regarded his case as due, not to the recent miliary tuberculosis, but to an occasional hematogenous metastasis to the liver and excretion into the bile of tubercle bacilli entering the blood from the severe tuberculous lesions of the genital tract. The only other case of gall-bladder tuberculosis that Beitzke could find in the literature was the one of Kisch. He quotes Kauffmann as saying that tuberculosis of the gall bladder is very rare, but that it may lead to the production of round, saccular or stellate ulcers that, extending through the wall, may lead to perforation. This statement likewise may be traced back to Kisch's case which showed a perforation into the colon.

In Simmonds' first article (1908) he calls attention to the extreme rarity of tuberculous lesions of the gall-bladder in spite of the fact that tuberculosis of the liver and intra-hepatic biliary passages is not rare, and that tubercle bacilli are frequently present in the bile. He could find in the literature only the four cases of Heddäus, Kisch, Schmidt and Beitzke mentioned above, all four of these cases presenting a severe caseous purulent cholecystitis with stone-formation. Acute miliary tuberculosis of the gall-bladder was not yet known. He reports a case of the latter condition in a nine-months old child showing countless miliary tubercles, bile-stained necroses and degeneration cysts in the liver. There was a generalized miliary tuberculosis of all organs, caseous bronchial and mesenteric glands, and tuberculous ulcers in ileum and colon. The gall-bladder was of normal size and the contents appeared normal. No tubercle-bacilli could be found in the latter. In the otherwise

normal-appearing mucosa there were six flat, sharply circumscribed areas, of the size of lentils, showing a marked bile-imbibition. Microscopical examination showed these to be areas of necrosis surrounded by a zone of granulation tissues. No tubercles or giant-cells were present, but the necrotic areas contained great numbers of tubercle bacilli at the border of the granulation tissue and caseous material. No tubercle bacilli were found in any other part of the gall-bladder wall. Simmonds believed the gall-bladder tuberculosis in this case to be wholly comparable with the execretory tuberculosis of the kidney-pelvis, tubercle bacilli passing into the intrahepatic bile-ducts and into the bile. Two forms of tuberculosis of the gall-bladder may result, a chronic ulcerative cholecystitis and the acute miliary tuberculous necroses of the mucosa.

Simmonds' case was presented before the meeting of the biologic section at Hamburg, in 1908, and in the discussion which followed, Deycke described a case which he personally had seen of empyema of the gall-bladder with a stone in the cystic duct. Animal inoculations showed the pus to contain tubercle bacilli, although cultures were sterile, and the microscopical examination showed diffuse tuberculous lesions in the mucosa.

Later Simmonds presented a second case of gall-bladder tuberculosis occurring in an 11 year-old child whose liver was thickly studded with tubercles and showed advanced tuberculosis of the intra-hepatic biliary passages. The mucosa of the gall-bladder contained numerous minute greenish sloughs of tuberculous necrosis containing tubercle bacilli. Simmonds regarded this case as a second one of excretory infection of the gall-bladder mucosa.

In his report of this second case, Simmonds adds another case of gall-bladder tuberculosis from the literature that of Knotte, 1907, who observed a tuberculous cholevstitis in a severe case of genera'ized tuberculosis. Knotte regarded a pre-existing cholecystitis as significant for the later tuberculous invasion. Cholelithiasis was not present in this case.

These eight cases of tuberculosis of the gall-bladder are the only ones that the writer has been able to find in an extensive survey of the German literature. While the French have given much attention to the study of tuberculosis of the liver and of the intraphepatic bile ducts, the great majority of the writers on these subjects make no mention of the gall-bladder. There exists one possible French case in the older literature, that of Gaucher (1870) who describes a case of tuberculosis of the liver in a child of three years of age, showing tuberculosis of lungs, pleurae, kidneys, spleen, mediastinal glands and intestines. In the liver the tubercles were arranged along the bile-bassages, while in the gall-bladder there was a "tuberculous mass as large as a hazel-nut." While the tuberculous nature of this lesion cannot be accepted as beyond all doubt, it may be regarded as a probable case.

The case reported by Lancereau is also a doubtful one, as the diagnosis is based upon gross appearances only. In an autopsy upon a woman thirty-two years of age a caseous mass replacing the gall-bladder was found. What were regarded as tuberculous granula-

tions were seen in the common duct and many "tubercles" were present in the spleen and mesenteric glands, and there was necrosis of a portion of the pubis. Lancereau regarded this case as one of primary tuberculosis of the gall-bladder.

In 1910, Galabrée reported two cases of tuberculous cholecystitis. The first case is doubtful, as no microscopic examination was made, and the gross pathological changes in the gall-bladder are very misleading. The second case is acceptable, as histologic examination of the thickened wall of the gall-bladder revealed many tubercles and tubercle bacilli. The patient was a woman, thirty-nine years of age, who had previously been perfectly well. For a month she had continuous sharp pain in the right side, increasing a few minutes after eating. There was a large abdominal tumor in the upper right side which was diagnosed as a kidney tumor. Posterior incision showed a normal kidney. Incision through the upper right rectus was made and the tumor was found to be transfixed gall-bladder containing one perforating stone and pus.

In 1911, Latronche collected four cases of supposed tuberculous cholecystitis and added one of his own. As only two of these cases had a microscopical examination, and as only in one were positive tubercles found,—that of Latronche, in which the tubercles were in the serosa of the gall-bladder as a part of a tuberculous peritonitis,—all of these cases can be excluded. The presence of a caseous pus in the gall-bladder is a very common event in old cases of empyema of this organ, and the fact that the pus appears caseous in character does not by any means stamp it positively as tuberculous in origin.

The only American cases of tuberculosis of the gall-bladder so far reported have been a preliminary report of the present case (the first American case) in the Transactions of the Western Surgical Association for 1925. In the Annals of Surgery for 1926, Rankin and Massie reported a case which they regarded as one of primary tuberculosis. The patient, a negress, aged thirty-eight, complained of pain and a mass in the right upper quadrant of the abdomen. History of pulmonary tuberculosis seven years ago. Clinical diagnosis of perforated duodenal ulcer with abscess formation. At operation a large mass was found adherent to liver and small intestine. When opened this was found to be the gall-bladder with walls about three-quarters of an inch thick, containing caseous pus but no stones. Microscopically, sections from the gall-bladder showed marked hyaline connective tissue thickening with dense infiltrations of lymphocytes and plasma cells, with a number of areas of necrosis surrounded by endotheloid and lymphoid cells with a few giant cells. Four years after the patient returned, showing shortness of breath, ascites and edema of feet. Clinical diagnosis was tuberculous peritonitis. Operation revealed abundant fluid in abdomen and peritoneum studded with tubercles. Although the microscopical description is not wholly convincing, this case is most probably one of gall-bladder tuberculosis, but the history and the association of an advanced generalized peritoneal tuberculosis make it doubtful that the gall-

bladder was the primary focus of the disease.

Rankin and Massie in reporting their case state that their search of the literature reveals only fifteen reported cases of primary tuberculosis of the gall-bladder. They include, however, the cases of Lancereau, the first case of Galabrée, the four cases (Broquehave, Tedenat, Riedel and Czerny) collected by Latronche, and the latter's own case, all of which we reject on the ground of insufficient evidence of the tuberculous character of the affection, or because the tuberculosis was evidently primarily peritoneal. This would reduce the number of reported cases of gall-bladder tuberculosis to eight undoubted cases (Heddäus, Schmidt, Kisch, Beitzke, Knotte, Simmonds, Deycke and Simmonds) at the time the preliminary report of our case was made in 1925. Counting these together and adding the case since reported by Rankin and Massie there are in the literature only ten reported cases of primary gall-bladder tuberculosis.

Since our case, the first one reported in America, has been published only in the Transactions of a limited society, it has seemed desirable to republish it here in fuller form, particularly since it had been missed in the survey of the literature given by Rankin and Massie.

Author's Case

Case No. 168-314—Female, age 59, housewife, referred to one of us (J. T. C.) by Dr. N. E. Knapp. Family history negative for tuberculosis. The patient suffered from spinal meningitis at the age of eighteen, followed by inflammatory rheumatism. There is a tendency to bronchitis, for which the patient has taken serum. Typhoid fever twice: first time thirty years ago, second time twenty years ago, followed by furunculosis. Operation for bad lacerations following childbirth. Peritonitis a few months later. Attacks of chronic appendicitis but no operation. Complete hysterectomy fifteen years ago for uterine fibroid. Severe headaches from puberty to menopause.

Summary of present ailment: Attacks of severe pain in epigastrium during the last year. Last attack followed by extreme exhaustion. The pain seldom extended to the right side but was accompanied by aching in the left upper abdomen, especially posteriorly, with the later attacks. The epigastric soreness was present more or less all the time, but was aggravated by movement, such as walking, or turning over in bed. Pain and stiffness in right knee, pain radiating to hip. Looseness of bowels, amounting at times to diarrhea. Soreness in rectum on bowel movement. Occasional stabbing pain in precordial region. Some palpitation and shortness of breath. Fatigue. Overweight, but has noted a loss of seventeen pounds during the last year.

Summary of Physical Examination: Height 62.1 inches. Weight 164 pounds. Temperature 98.4° F. Pulse 72, reclining. Blood pressure: systolic 135, diastolic 85. Rather heavy frame. Overweight. Muscles rather flabby. Joints not swollen. Crepitation in right knee. Skin and mucous membranes a trifle pallid. No enlarged glands palpable. Pupils react promptly to light. Tongue slightly coated. Chronic pharyngitis. Pyorrhea. Tonsils removed. Chest well developed, and expansion good. Breasts normal. Lungs normally resonant. Respiratory sounds normal except for some harsh breathing at the bases. No pulmonary congestion. No definite râles. The apex beat neither seen nor felt. Cardiac diameter 9.5 cm. to the left, but does not extend beyond the right sternal border. Heart sounds fairly distinct. No edema of lower limbs. Liver dullness normal. Splenic dullness not increased. Epigastric percussion and palpation gave considerable discomfort. Marked abdominal tenderness.

X-ray Examination with Opaque Meal: Stomach normal as to function and appear-

ance, except for moderate delay in the emptying time (a quarter of the meal remaining at the sixth hour). No abnormality in small intestine. Multiple diverticula of colon, especially the pelvic loop, but without indications of colonic obstruction.

Laboratory Findings: Urine normal.

Blood: Hemoglobin 87. Red cells 4,630,000. White cells, 5,100. No differential bloodcount made. Non-protein nitrogen 31.1. Uric acid 4.0. Blood sugar 110. Alveolar CO_2 tension 33.

Fecal examination showed a bad flora predominating but no other unusual findings.

Gastric juice analysis: Considerable bile in gastric contents. Marked hyperacidity, both total and relative.

Surgical Consultation: Resulted in a definite diagnosis of chronic gall bladder disease with gall stones and a recommendation for operation.

Operation: July 18, 1924 (by J. T. C.) in the Hospital of the Battle Creek Sanitarium. The gall bladder was found buried in adhesions, very dense in character and separated only with the greatest difficulty. The adhesions involved all the neighboring structures. The liver appeared smooth and normal except for the pericholecystic adhesions. The gall bladder, which contained one large stone the size of a pigeon's egg, besides a soft indeterminate mass in the fundus, was removed with as wide dissection as possible including a part of the liver substance, and a drain was tied into the cystic duct. The stomach and duodenum seemed normal, except for the adhesions. No stones were palpable in the common duct. Pancreas normal to palpation.

When the gall bladder was opened, there was found within it a friable degenerating mass which strengthened our already strong suspicion of a malignant process.

The postoperative convalescence was stormy. The temperature reached as high as 103° on the second day and remained high for two more days. There was a very free drainage of bile-stained material from the wound and the dressings had to be changed frequently. On the sixth day the drainage material looked so much like duodenal contents that we made a test by giving the patient in the morning capsules containing carmine; in the evening there was carmine on the gauze dressings, thus making sure a diagnosis of duodenal fistula. The patient's temperature dropped to normal on the seventh day and remained approximately normal during the remainder of the convalescence. The skin was protected with animal charcoal, a treatment which later caused trouble; for many months after the operation an abscess developed in the abdominal wall which cleared up promptly after the evacuation of pus and a quantity of charcoal. The stool was free from bile on repeated tests.

During the next ten days the patient at times developed a condition of mental confusion, urinary retention and irregular pulse, which made us despair of her recovery, but under repeated intravenous injections of glucose and Ringer's solution these symptoms passed.

Every device for closing the duodenal fistula failed, including the application of constant suction of the excoriating juices from the wound. The passage of a duodenal tube was proposed but only on the twenty-first day did the patient finally consent. An ordinary duodenal tube was then passed through the stomach and duodenum well into the upper jejunum. The drainage through the fistula at once diminished, and ceased almost entirely within seventy-two hours. On the fourth and fifth days the wound was absolutely dry when dressed, all skin irritation having subsided. Nausea and other unfavorable symptoms were absent, except that once or twice daily, following the introduction of the duodenal tube, the discomfort of the tube caused the patient to vomit a little bile, this being the first time that bile had passed into the duodenum. The presence of the tube disturbed the patient so much that nausea began to reappear, so that on the thirtieth day after the operation, nine days after its introduction, the duodenal tube was removed. From then on the patient's recovery was uneventful.

Let us remark here, in connection with the duodenal fistula, that introduction of the duo-

denal tube within a day or two of the diagnosis of duodenal fistula would undoubtedly have shortened this patient's convalescence by at least 100 per cent and made unnecessary a later operation for abdominal hernia. The value of the duodenal tube lying well into the upper jejunum in this type of case is analogous to the usefulness of an inlying catheter in an immediate after-care of cases of vesico-vaginal or other forms of vesical fistula. The literature contains little mention of this means of treatment for duodenal fistula, two cases by Einhorn and one or two others being the only ones available in a cursory search of the literature.

A letter from the husband sixteen months after the operation reported that the patient's general health was good and that there had been no return of the abdominal symptoms.

The *pathologist's report* (A. S. W.) on the specimen removed (U. of M. No. 301-AC) follows:

Gallbladder: Small with greatly thickened wall, containing a large, oval, pigment and cholesterin calculus. At the mouth of the gall-bladder the cavity is completely obliterated by a mass the size of a hickory nut. The cystic duct is likewise very much thickened and partly obliterated. Besides the stone, the cavity of the gall-bladder contains caseous pus.

Microscopic examination: Mucosa almost entirely replaced by caseating tubercles. Only toward the neck of the bladder are there any remains of the glands of the mucosa. The greater part of the mucosa of the fundus consists of a caseating tuberculous ulcer. Throughout the entire wall are scattered caseating miliary tubercles. In some areas the tuberculosis of the musosa extends deep into the wall, forming deep fistulous tracts, lined with caseous epithelioid tissue. Giant cells are numerous in the smaller tubercles. Toward the neck of the bladder portions of the glandular mucosa are preserved showing numerous tubercles arising in the mucosa between the glands. The muscularis and subserosa of the bladder wall show marked fibrosis, and a few small miliary tubercles are found in the subserosa—none on the peritoneal surface. The process diminishes in intensity from the mucosa towards the serosa.

Pathological Diagnosis: Chronic tuberculosis of the gall-bladder. Chronic tuberculous cholecystitis.

COMMENT

The eight older cases fall into the two groups of the classification proposed by Simmonds and accepted by Aschoff:

Chronic tuberculous cholecystitis..6,
4 of these with cholelithiasis.
Acute miliary tuberculous necrosis 2

Our case was one of chronic tuberculous cholecystitis associated with cholelithiasis; that of Rankin and Massie was the same without any calculus. Five of the eight cases then of chronic tuberculous cholecystitis were associated with cholelithiasis; three were not. From this association the presence of calculi can hardly be regarded as significant in lowering the gall-bladder resistance to tubercle bacilli entering through the bile. The calculi may be either primary or secondary to the infection, and it is impossible from the data at hand to say which. There is nothing distinctive in the symptomatology of gall-bladder tuberculosis, and it is very unlikely to be recognized clinically when it is primary and confined to the gall-bladder. Its diagnosis will rest wholly upon the

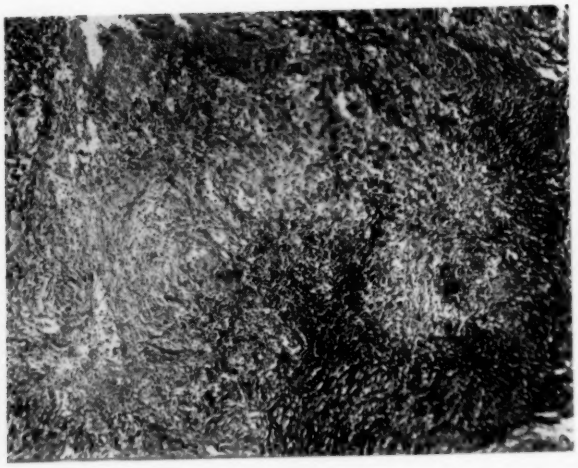


FIGURE 1. Low power of gall-bladder wall, showing base of tuberculous ulcer of mucosa. Caseating border of epithelioid tubercles.

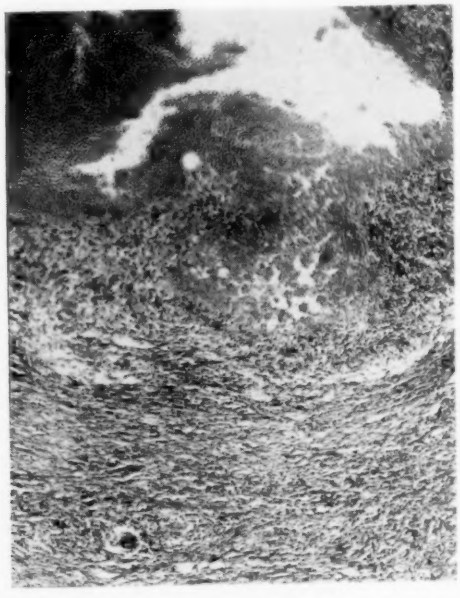


FIGURE 2. Low power of gall-bladder wall, showing caseous ulceration of epithelioid tubercles replacing the mucosa.

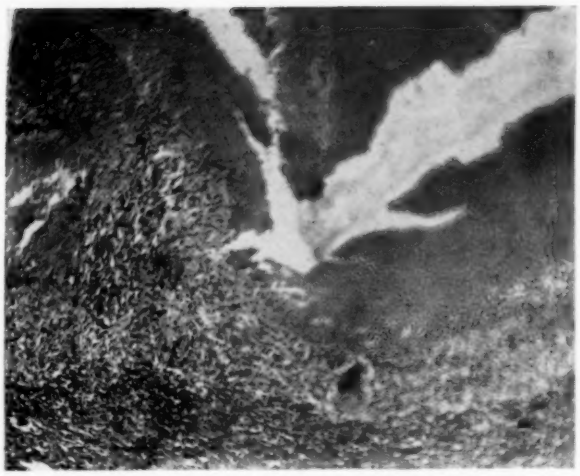


FIGURE 3. Higher power of caseous ulcer of mucosa of gall-bladder. Epithelioid zone with giant cell.

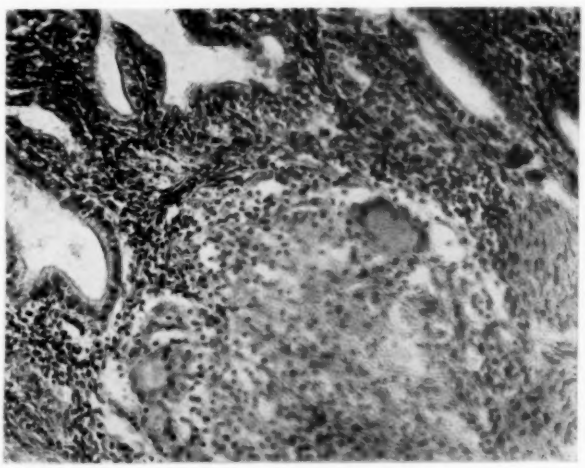


FIGURE 4. Non-ulcerated portion of gall-bladder mucosa showing epithelioid tubercles in stroma of glands.

FIGURE 5. Miliary tubercles in gall-bladder mucosa.

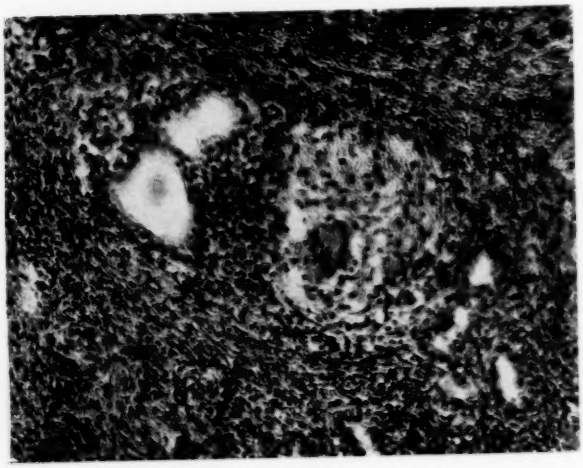


FIGURE 6. Higher power view of miliary tubercle in gall-bladder mucosa with atrophy of mucosa.

findings of the pathologist, and the condition because of its extreme rarity must be regarded as a pathological curiosity. The most interesting point about it is the theoretical explanation of its rarity. Why does the gall-bladder escape tuberculous infection to so much greater extent than the pelvis of the kidney, for example? All of the evidence points to a high degree of immunity to the tubercle bacillus on the part of the gall-bladder mucosa. The relationship of the bile itself to this immunity is a factor to be considered, but we do know that tubercle bacilli contained in bile do not lose their virulence in animal experimentations. Rankin and Massie say that all of the reported cases have been in females; this is an error, as Beitzke's case (1905) was that of a 57-year-old male. It is very probable that all of the cases of gall-bladder tuberculosis are associated with tuberculous lesions, either active or latent, elsewhere in the body, and that the involvement of the interior of the gall-bladder is of the nature of an excretory infection by way of the biliary passages. The possible involvement of the peritoneum in all cases of gall-bladder tuberculosis must be always borne in mind. As to treatment, cholecystotomy should be performed in any case in which, at operation, a suspicion of gall-bladder tuberculosis arises.

Conclusions

Tuberculosis of the gall-bladder is a very rare affection. It has no clinical entity, and cannot be differentiated clinically from other forms of cholecystitis. Its diagnosis rests wholly upon the pathological examination. The mucosa of the gall-bladder possesses a very high degree of immunity against infection by the tubercle bacillus. When such an infection does occur it is probably always an excretory infection, by way of the bile, of bacilli arising from some other tuberculous focus, latent or active, within the body.

BIBLIOGRAPHY

Simmonds: Centralbl. f. allg. Path. u. Anat., 1908, xix, 225; Münch. med. Wochenschr., 1908, LV, 1049. (Cites cases of Heddäus, Kisch, Schmidt and Beitzke.)

Deycke: Sitzung d. biol. Section, Hamburg, 1908; Ref. Münch. med. Wochenschr.

Knotte: Inaug. Dissert, Leipzig, 1907.

Gaucher: Bull. de la Soc. d'Anatomie, 1879, 515.

Case and Warthin: Transactions of Western Surgical Assoc., 1925, 171.

Rankin and Massie: Annals of Surgery, 1926, LXXXVI, 800.

O-iodoxybenzoic Acid in the Treatment of Infectious Arthritis; Report of Eighty Additional Cases*

By John B. Youmans, M.D., *Nashville, Tennessee*

In a previous communication (1) A. G. Young and the author reported the results obtained in a series of forty-three patients with infectious arthritis treated with O-iodoxybenzoic acid. Since then Smith (2) has reported his results with the drug in a series of thirty-three patients. The present paper is a study of eighty additional cases treated at the University Hospital since the first report and includes all patients who have been under observation for a period sufficiently long to warrant an estimate of the amount of improvement gained. All of them have been under observation for a period of at least six months; thirty-three have been under observation for a year or more.

In some important respects the present series differs from that of the first report. The patients included in this series are not a group selected, treated and studied solely by the author. Instead the group includes patients of various members of the staff, selected by them in the ordinary course of practice for the treatments. To a large extent the patients were not treated personally by the author but received their treatments in the clinic under the author's supervision, a special treatment clinic having been established for that purpose. Such a proceedure was made necessary by the large number of patients to be treated and while to some extent it influences unfavorably the results of treatment, because of the lessened personal attention given individual patients, it gives a more uniform estimate of the improvement generally to be expected as the result of treatment under average circumstances. Also, under this arrangement the estimate of improvement gained has been based to a considerable degree on the opinions of more disinterested observers.

The distribution of the cases in respect to age, duration of disease, degree of crippling or deformity and type of arthritis is shown in Tables II to V inclusive. As in the previous report the extent of deformity or crippling has been based on the amount and kind of relatively permanent change present such as bony or fibrous ankylosis, subluxations, muscular atrophy, tendon and muscle contractions and the like, not on the basis of deformity or loss of function due to pain,

*From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor.

swelling, tenderness, muscle spasm, etc. The classification of the various forms of arthritis has been based on the usual diagnostic criteria including the roentgenologic findings. In classifying the various forms of arthritis the author has considered the degenerative (hypertrophic) form to be infectious, at least in part. The presence of both degenerative and proliferative (hypertrophic and atrophic) changes in the same patient, to which further reference will be made later, has to some extent influenced this decision.

Method of Treatment

The method of treatment was in general the same as that previously employed. However, not all the patients were hospitalized, a large number being treated as ambulatory patients in the Out-Patient Department in the special treatment clinic mentioned above. O-iodoxybenzoic acid in the form of the ammonium salt (ammonium iodoxybenzoate) was given intravenously in doses of one gram in one per cent solution (100 cc. of a one per cent solution). The drug was prepared by dissolving it in warm, sterile, freshly distilled water. For convenience in treating a large number of patients the total amount to be used in one day was prepared in bulk and generally passed through a Berkefeld filter. Single doses were prepared by simply dissolving the drug in the proper amount of water as described above. As stated in the former paper the solution should not be boiled and should be used within two hours after being prepared. It was administered intravenously, at body temperature, by the gravity method over a period of seven minutes or more, following the precautions usually observed in intravenous therapy.

Treatments were given twice a week, six to ten treatments (generally eight) constituting a "course." Ordinarily from one to three courses were given with intervals of from two to eight weeks between courses, but in some instances longer periods of time were allowed to elapse between courses because of the failure of patients to return on time. In a few instances less than one course of treatment was given. Three patients received three or more courses. Two of the latter were treated partly by means of rectal administration. For administration by rectum doses of two grams in two per cent solution were employed, the courses consisting of ten to twelve injections.

Some of the patients received treatment other than the drug. For the most part this consisted of baking and massage, but two patients were treated with diathermy and one received sufficient thyroid extract to raise the basal metabolism to normal and hold it at that level. In practically every instance this supplemental treatment was used in such a way as to permit a separate estimate of the amount of improvement secured by it. Generally speaking this treatment was insufficient in amount to influence the course of the disease. Prophylactic orthopedic measures which were freely used for the prevention of deformities are not classified with these other forms of therapy. Orthopedic treatment for the relief of deformities was employed in some cases in connection with the use of O-iodoxybenzoic acid but in

such a manner as to allow easy distinction between the relief obtained by it and by the drug. Reference is made elsewhere to this combined use of orthopedic surgery and O-iodoxybenzoic acid.

The greater number of the patients treated had had all obvious foci of infection removed before coming under our care. In the case of those who had not, such apparent foci were removed and the effect observed preliminary to treatment with the drug. Those patients confined to the hospital received simple medical care and their activity was governed by the extent of their disability. Active motion was encouraged. Analgesics, which were sometimes required at the beginning of treatment, quickly became unnecessary in the successful cases. Most of the patients had previously been treated adequately or inadequately by a variety of methods.

Results

The results in general are summarized in Table I. It is seen that of the entire 80 cases, 45 or 56 per cent were markedly improved, 13 or 16 per cent, moderately improved, 10 or 13 per cent, slightly improved, and 12 or 15 per cent, were unimproved.

Table I.

Treatment with O-Iodoxybenzoic Acid. Summary of Results.

Improvement	No. of Cases	Per Cent
Marked	45	56
Moderate	13	16
Slight	10	13
None	12	15
Total	80	100

As in the previous report the amount of improvement is guaged by the results in each individual case since improvement is entirely a relative factor depending on the circumstances in each separate patient. Obviously, loss of pain and partial restoration of function in a helpless cripple is a much greater improvement for him than for one who already possesses a considerable degree of functional integrity. As in the first series reported improvement has been taken to mean loss or diminution in pain, swelling and tenderness, increased function and improvement in general health.

The degree of improvement as related to the various groups as classified is shown in Tables II to V inclusive. Table VI shows the relation of improvement to the amount of treatment received.

Table II.

Treatment with O-Iodoxybenzoic Acid. Age of Patients and Relation to Improvement Gauged

Age Groups	No. of Cases	Improvement: Marked	Moderate	Slight	None
10-19	6	5		1	
20-29	25	15	2	5	3
30-39	19	12	3		4
40-49	20	10	6	2	2
50-59	7	3	1	1	2
60-69	3		1	1	1
Total	80	45	13	10	12

Discussion

An analysis of the kind of improvement received is of value and may have a bearing on the action of the drug in this disease. Relief of pain continues to be the most common and outstand-

TABLE III.

TREATMENT WITH O-IODOXYBENZOIC ACID. AMOUNT OF CRIPPLING AND RELATION TF IMPROVEMENT GAINED

Crippling	No. of Cases	Improvement: Marked	Moderate	Slight	None
None	23	17	2	1	3
Slight ...	25	14	3	4	4
Moderate	22	11	6	2	3
Marked...	10	3	2	3	2
Total	80	45	13	10	12

TABLE IV.

TREATMENT WITH O-IODOXYBENZOIC ACID. DURATION OF DISEASE AND RELATION TO IMPROVEMENT

Duration of Disease	No of Cases	Improvement: Marked	Moderate	Slight	None
Acute	9	8			1
6 mo. to 1 yr.	10	4	3	1	2
1 to 2 yrs. .	14	9	1	2	2
2 to 5 yrs .	27	16	6	2	3
5 to 10 yrs. .	8	2	1	2	3
Over 10 yrs. .	12	6	2	3	1
Total	80	45	13	10	12

ing result secured. In a large majority of the patients receiving improvement the great decrease or disappearance of pain, which in many cases had been present for years, constituted the most outstanding relief obtained. Even in those cases in which only partial improvement occurred relief from pain was frequently secured. So frequent and marked has been this effect that it alone in some cases has been considered adequate justification for the

TABLE V.

TREATMENT WITH O-IODOXYBENZOIC ACID. TYPE OF ARTHRITIS AND RELATION TO IMPROVEMENT

Type of Arthritis	No. of Cases	Improvement: Marked	Moderate	Slight	None
Simple (acute)..	8(*)	6	2		
Gonorrhoeal.....	9(*)	6		2	1
Hypertrophic..	15(*****)	7	3	2	3
Atrophic.....	54(*****)	29	10	6	9
	86				
Duplicate	6				
Total	80				

*Duplicate (Mixed) Cases.

TABLE VI.

TREATMENT WITH O-IODOXYBENZOIC ACID. AMOUNT OF TREATMENT AND RELATION TO IMPROVEMENT.

Amount of Treatment	No. of Cases	Improvement: Marked	Moderate	Slight	None
Less than one Course	8	2	1	1	4
One Course	33	20	3	4	6
Two Courses	36	21	8	5	2
Three or more Courses	3	2	1		
Total	80	45	13	10	12

use of the drug, and in some instances it was employed for this purpose even though there seemed little likelihood of any other improvement.

In addition to relief of pain the increase in function, principally increased range of motion, was frequently striking. As previously noticed, such increase in function in patients consid-

ered to have quite permanent fixations and deformities suggests that such fixations and deformities are not infrequently less permanent than they apparently seem. Increased function due to relief of pain, swelling, effusion, muscular spasm and tenderness were naturally still more frequently encountered.

Of particular interest has been the improvement in the general health. This was manifested not only by the disappearance of fever and other signs of infection but especially by a gain in weight, increased appetite, improved color, and by a feeling of general well being and a changed mental attitude. An increase in weight during and following treatment was a nearly constant feature of the improvement. Further evidence of improvement in the general health was noted in the disappearance of trophic changes in the skin, nails and hair, reestablishment of menstruation and loss of muscle atrophy. With the latter there was an increase in strength and an improvement in function which was in turn itself responsible for an increase in muscle strength and tone. The observation of these changes has suggested to the author that they are not due solely to the disappearance of the infection but to a definite action of the drug.

Attention should be called to the advantageous use of the drug in connection with orthopedic surgery. By its use prior to operative and non-operative procedures it has, by reducing pain, swelling and spasm and by diminishing the activity of the infectious process, not only favorably influenced the result of such procedures but in some instances made possible their use. The use of the drug subsequent to operation has decreased the likelihood of a post-operative flare-up of the disease and has favored an early and more extensive return of function. Thus better results have been accomplished by the combined treatment than by either method alone.

Ordinarily improvement occurred, if at all, after the first few injections, generally earlier in the more acute cases and more slowly in those of longer standing. In some instances improvement was delayed until the end of the first course and in a few instances no improvement was noticed until some time after the completion of the first or even the second course. In the latter instances the patients, who were discharged at first without evidence of improvement, later returned showing definite beneficial effects of the treatment. In all cases the final improvement as recorded has been maintained at practically the same point to the present time.

A consideration of the improvement gained, based on the age groups, indicates that better results are obtained in the younger patients as was also the case in the first series. Such greater improvement is not due to occurrence of a milder form of arthritis at a younger age since the most severe forms occur in early and middle life. It seems definitely related to such factors as increased general resistance, better general health and in particular better and more adequate function of the circulatory system. Old age itself however constitutes no absolute bar to improvement and of the 10 patients 50 years old or more, five were markedly or moderately improved.

As stated in the first report the degree of permanent or semi-permanent deformity or crippling bears more importantly on the likelihood of improvement than any other single factor, as might be expected. Of the 45 patients with little or none of this type of deformity or crippling, 31 or 68 per cent were markedly improved; of the 32 with marked or moderate deformity 14 or 43 per cent were markedly improved. It is true that in many of the latter cases the deformity was of a mechanical nature which naturally could not be expected to respond to drug therapy and required mechanical (orthopedic) treatment which should of course be employed in these cases in conjunction with the drug. Moreover it should be born in mind that such deformities in themselves tend to favor the persistence of the infectious process and their correction, often times made possible by the preliminary use of the drug, has been of great aid in securing a general improvement in the disease. Reference has already been made to improvement gained by the drug alone in the case of patients thought to have relatively permanent deformities. In such cases one cannot but conclude that the crippling was less permanent and mechanical than had been thought.

The duration of the disease is of importance in regard to improvement only in so far as it is related to the occurrence of the deformities referred to above. Long duration in itself is of no particular significance (if acute cases are excepted) and of the 12 cases in which the disease had lasted ten years or more six or 50 per cent were markedly improved. Most of the cases of simple (acute) arthritis were greatly improved as might be expected, since many of them improve spontaneously or with a variety of forms of treatment. O-iodoxybenzoic acid however did seem of value in the acute cases by giving more prompt improvement than the usual methods and seemed of particular value in these cases which showed a tendency to become chronic. The gonorrhoeal cases especially, which frequently exhibit this tendency to chronicity, were markedly benefited in most instances.

Considering the various forms of arthritis, the largest group was that of the atrophic (proliferative) variety. This group showed generally more improvement than the group of hypertrophic (degenerative) arthritis. However seven of the 15 cases of the latter type showed marked improvement, a larger number than were expected from the experience of the previous series. Included in this group were a number of cases with extensive involvement of the spine (spondylitis rhizomelica) and the degree of improvement in some of these cases, particularly the disappearance of pain, and increased range of motion, was surprising. In general however such cases offer a less hopeful prognosis than is the case with the atrophic (proliferative) variety. To some extent this is undoubtedly due to the more frequent occurrence of the hypertrophic (degenerative) form in old persons, in whom disturbances in circulation influence adversely the progress of the disease and the results of treatment. Attention has already been called to the occurrence at times of both proliferative and degenerative

changes in the same patient. It seems possible that the presence of atrophic (proliferative) changes, which more readily respond to the drug, may explain the unusual improvement seen in some of the cases classified as hypertrophic arthritis.

Of particular importance is the relation of the degree of improvement to the amount of treatment as shown in Table VI. The association of greater improvement with more treatment is natural and is seen in many diseases but it should also be borne in mind that those patients receiving the greater amount of treatment were in general patients with the more severe forms of the disease. On the whole the patients in the series here reported received more treatment than those of the previous series since the use of eight treatments to a course was more general. It is worth noting that of the 36 patients receiving two or more courses of treatment, and who may, in general, be assumed to have a more severe form of disease, 58 per cent showed marked improvement as contrasted with 60 per cent in the group receiving but one course and who, as a group, were probably less severely affected. Of the three patients who received three or more courses of treatment, and who had a very severe form of the disease, two obtained marked improvement.

A study of the failures is important and valuable in any attempt to determine the value of a given form of treatment. In Table VII is summarized certain data regarding the 12 cases in whom no improvement whatever was obtained. In six cases treatment was inadequate for one reason or another. In two cases active disease was absent, mechanical deformities alone remaining. In one case it was questionable whether arthritis (sacroiliac) was actually present and malingering was suspected. The remaining three patients simply failed to show improvement without any apparent cause for the failure. The case of the patient who developed hematuria while under treatment is discussed more fully below. In no case was any patient made worse, temporary reaction from the treatments excepted.

Table VII.

Treatment with O-Iodoxybenzoic Acid. Summary of Data in Cases Showing No Improvement

	No. of Cases.
1. Treatment Incomplete (Refused 2; Pneumonia 1; Hematuria 1)	4
2. No Active Disease (Deformities only)	2
3. Failure to Cooperate	2
4. No Disease (Malingerer)	1
5. No Explanation (one course, 1; two courses, 2)	3
Total	12

Methods of Administration

As stated above, the patients in this series were given the drug intravenously. Smith in his first paper (2) reported considerable success from its use by mouth and by rectum but later (3) stated that he had found it much more effective given intravenously. Observations by the author are as yet too incomplete to warrant a conclusion as to the value of the drug by mouth. It is undoubtedly effective to some extent and can be given without any particular discomfort but so far it has not appeared to be sufficiently effective to warrant its use by mouth in-

stead of intravenously. From the experience gained thus far it has seemed best to use it intravenously whenever possible and if not to use it per rectum. Rectal administration has the advantage of permitting its use by the patient at home and it is possible that treatment per rectum may be worth while as supplementary treatment between courses of intravenous treatment.

One gram (intravenous) has proven the most effective average dose although larger doses (1.5 grams) may be given in most cases without ill effect and smaller doses may be advisable at times, particularly on starting the treatment and in those specially sensitive to the drug. Bi-weekly treatments are to be recommended since more frequent use tends to cause gastro-intestinal disturbances and less frequent treatments are definitely less effective. No necessity exists for limiting the courses of treatment to eight or ten injections and longer courses may be given if desired. Courses of eight treatments were selected largely on the basis of economic factors and four weeks has proven to be a fairly satisfactory period for active treatment in the average case. Likewise six to eight weeks seems to be a suitable rest period in most instances. Treatment should however be individualized according to the needs of each patient, providing caution against insufficient treatment is observed. Treatment per rectum should, to be effective, be employed over a longer period than in the case of intravenous treatments. It should be emphasized however that references to treatment per rectum should not be construed as a recommendation of that form of treatment over treatment by vein in cases where the latter method can be employed.

Action of the Drug

No attempt will be made in this paper to discuss the action of the drug except for its bearing in a small way on certain clinical observations. As Smith has pointed out, the drug possesses a salicylate like reaction which is of interest in view of its structural similarity to salicylic acid. However, studies not to be reported here in detail show definitely the absence of any excretion of salicylate in the urine. Although it contains an atom of iodine the absence of iodism associated with the use of the drug suggests a lack of any ordinary iodide effect.

Its resemblance to the salicylates is most noticeable in its analgesic effect although the latter seems more powerful and lasting than is the case with salicylates. However the drug seems to have other and more delayed actions, particularly that associated with improvement in the general health. It seems possible that these effects may be associated with its action on antibody formation described by Hektoen (4) and Arkin (5).

Clinical observations suggest a relation between its action and changes in the circulation, observations which are of particular interest in the light of recent studies on the effect of circulatory changes in joint disease (6). If this be true it is apparent that although it may prove to be effective generally in arthitis associated with pain, swelling and spasm, the extent of its beneficial action may vary in different forms of arthritis according to the

circulatory changes present, as has been observed clinically. On such a basis may be explained its lessened effectiveness in the degenerative forms and in other types of arthritis in old people.

Reactions

No serious reactions were encountered in any of the cases. Nearly all the patients experienced the immediate reaction described in the previous report. Briefly it consisted of burning and stinging in the eyes, nose and throat and at times over the entire body. Most patients described it as similar to the sensations associated with eating mustard or pepper. Lacrimation frequently occurred and occasionally salivation. Flushing, sweating and tingling in the extremities were associated symptoms. Not infrequently patients complained of increased pain in the affected joints which sometimes lasted for twelve to twenty-four hours and was usually interpreted as a favorable sign. Occasionally a sense of suffocation or of pressure in the sternal region was noted. Nausea was rather frequent and occasionally there was vomiting. The latter symptom was very variable and some patients would take nearly a whole course without difficulty only to vomit with the last injection. Others vomited with the first treatment but not subsequently. Both eating and abstinence from food before treatment influenced this symptom favorably in different patients. While vomiting, if it occurred, was usually associated with the immediate reaction it occasionally was delayed an hour or more. In two cases a slight diarrhoea was noted the day following treatment on one or two occasions. A few patients complained of drowsiness the afternoon of the day following the treatments.

A late reaction, consisting of chill and fever occurring one half to two hours after injection, was noted in many of the acute and some of the chronic cases. In the author's experience this late reaction with chill and fever has been associated with a febrile type of the disease and other signs of an active infection. With improvement such patients became fever free and failed to develop this type of reaction. There is no evidence that improvement or the action of the drug was necessarily dependent on the occurrence of this febrile reaction and improvement without it was common.

The immediate reaction described above was usually over within a few minutes to an hour and most of the patients were able then to resume their usual activities. Some of the ambulatory patients returned to work. Those who reacted more severely were more or less incapacitated for twelve to twenty-four hours but practically all such were comfortable the next day.

In no case in this series were the reactions sufficiently severe to lead us to discontinue treatment and but one such case has occurred in all the patients treated. In the latter case (not included in this series) a rash, of the nature of a toxic erythema, appeared after the first treatment and was accompanied by rather severe nausea, vomiting and diarrhoea. The rash disappeared promptly and a second treatment caused no return but was followed again by a gastro-intestinal dis-

turbance. This and the mental reaction of the patient led to the discontinuance of treatment, a decision influenced partly by the fact that the patient had already received considerable improvement. Only two patients in this series refused further treatment because of the severity of the reactions and in neither instance did the reactions seem, objectively, particularly severe. On the contrary practically every patient has been anxious to continue the treatments, sometimes insisting even when it was felt that no further benefit could be secured. We are consequently at a loss to explain the apparently severe reactions reported to us by some users of the drug although it is probable that some of the reactions encountered during the early use of the drug were due, as suggested by Smith (2), to decomposition products resulting from the use of the free acid. The use of the stable ammonium salt has undoubtedly contributed to reducing the occurrence of severe reactions and Smith in a second communication (3) reported much less severe reactions using the ammonium salt than he had observed with the free acid.

Three patients, not included in this series, but including the case referred to above, developed a skin rash of the nature of a toxic erythema. In two cases it followed the first injection and in the other it occurred after four or five treatments had been given. In all it disappeared in two or three days, and subsequent treatment was not followed by a reappearance of the rash. In no case were the symptoms of iodism observed.

The occurrence of thrombosis of the vein at the site of injection has continued to be an unpleasant feature. Its frequency has been lessened by the use of the ammonium salt and can be further lessened by careful technique and by washing the drug into the vein with physiologic salt solution. Individual susceptibility to thrombosis as noted in the previous report is an important factor, and the occurrence of thrombosis is also related to the size of the vein and the rate of injection, probably on the basis of physical trauma and dilution factors. The frequent necessity of using small superficial veins in many of the patients, particularly those in the more deforming stages of the disease, tends to make such unfortunate occurrences more common. In no case however has a slough or other severe injury occurred, even when the drug has been accidentally injected outside of the vein wall, and a sore arm for a few hours with a subsequently occluded vein (temporary or permanent) has been the only ill effect observed.

The occurrence of gross and microscopic hematuria during treatment in one case (Table VIII) led to discontinuance of treatment. Such an occurrence would be of particular importance were it thought to be the effect of the drug. However, since such a phenomenon has never been encountered in any other case and since discontinuance of treatment had no effect on the hematuria and there were no other signs of renal injury it was not thought to be the effect of the drug.

No specific contraindications to the use of O-iodoxybenzoic acid have been found but in general it has not been used, nor does its use seem advisable,

in such conditions as nephritis, heart failure, diabetes, tuberculosis, thyrotoxicosis and the like.

It should be unnecessary to state that in the treatment of arthritis, as in any disease, all measures that benefit the patient should be employed and reliance should not be placed on single measures alone if more than one form of treatment is indicated. Attempts to remove the cause of the disease should be made whenever possible. In the case of the patients in this study further opportunity has been given to observe the need for close cooperation with the orthopedist in the management of these cases. Reference has already been made to the use of curative and prophylactic orthopedic procedures in combination with the use of O-iodoxybenzoic acid. Protective measures in particular are necessary, not only to prevent deformities due to the effects of the disease but to guard weakened joints, muscles, tendons, etc., as these parts again become functionally active. It is to be remembered that such injured structures offer decreased resistance not only to infection but also to mechanical injury from use. Proper footwear, avoidance of occupational strain, restriction of activities to within the limits of tolerance, proper appliances, etc., are all essential for securing the maximum of improvement and particularly that type of improvement which could not be expected to result from the use of the drug alone.

Summary and Conclusions

Of 80 patients with infectious arthritis treated with O-iodoxybenzoic acid nearly three fourths were markedly or moderately improved; the remainder showed little or no improvement. No serious untoward effects were noted.

These results substantiate the findings of an earlier report by A. G. Young and the author. Further evidence is given that O-iodoxybenzoic acid is of value in the treatment of infectious arthritis and in the opinion of the writer the results obtained by its use under comparable circumstances, are superior to those obtained with other forms of medical treatment. It is believed that a continued and more extended trial of the drug is warranted in order that its ultimate value be ascertained.

Note

Since this paper was written Trauba has reported (7) the results in 31 cases of chronic arthritis treated with O-iodoxybenzoic acid. His results, while not as favorable as those previously reported, are encouraging, particularly in view of the type of case treated and the amount of treatment given.

It should be pointed out, however, that because of the variety of modes of administration used his results should not be compared directly with those in which the drug was given almost solely by the intravenous route. Also, treatment in many of Trauba's cases would probably be considered insufficient. Of the 19 cases in which little or no improvement was obtained, treatment was probably incomplete in 15 and of these 11 received less treatment than was advised in the original report by Young and Youmans.

BIBLIOGRAPHY

(1) Young, A. J. and Youmans, J. B.: The Use of O-iodoxybenzoic Acid in the Treatment of Infectious Arthritis, J. A. M. A. 87:746. (Sept. 4) 1926.

(2) Smith, Millard: The Use and Action of O-iodoxybenzoic Acid in the Treatment of Arthritis, Bost. M. and S. Journal. 196:305 (Feb. 24) 1927.

(3) Id.:The Use and Action of O-iodoxybenzoic Acid, Boston M. and S. Journal 196-540 (Mar. 31) 1927.

(4) Hektoen, Ludwig: Proc. Chicago Path. Soc. 8:138, 1911.

(5) Arkin, A.: The Influence of Certain Oxidizing Agents (Sodium Iodosobenzoate and Sodium Iodoxybenzoate) on Phagocytosis, J. Infect. Disease 11: 427, 1912.

Id: The Influence of an Oxidizing Substance (Sodium Iodoxybenzoate) on Immune Reactions, Infect. Disease. 16:349. 1926.

(6) Pemberton, R.: The Etiology and Pathology of Arthritis, J. A. M. A. 87:1253 (Oct. 16) 1926.

(7) Trauba, N. C.: O-iodoxybenzoic Acid in Treatment of Chronic Arthritis. J. A. M. A. 89:1124 (Oct. 1) 1927.

The Histopathology of the Tonsil in Acute Rheumatic Fever and Chorea*

By W. W. G. Maclachlan, M.D., and deWayne G. Richey, M.D., *Pittsburgh*

THAT there is often a close clinical relationship between tonsillitis and acute rheumatic fever is an established fact. With this in mind, many individuals have conducted investigations relative to the bacteriological and pathological aspects of both tonsillitis and rheumatic fever. Inasmuch as the scope of the subject at hand has not embraced a consideration of its bacteriologic phases, our interest in the results of these endeavors has centered around those appertaining to the histopathological pictures obtained in the various tissues of man, and of the experimental animal. In this regard the recent work of Clawson, (1) who has demonstrated in the rabbit that "nodular inflammatory areas showing a cellular reaction similar to that found in human Aschoff bodies are produced in these cases of myocarditis," has been in agreement with the views to those who believe that the streptococcus viridans group is intimately associated with the etiology of acute rheumatic fever. On the other hand, Miller (2) has encountered lesions containing lymphocytes and endothelial leucocytes in sixty per cent of apparently healthy, adult rabbits used as controls in an experimental study on the transmission of the virus of rheumatic fever.

Since Aschoff (3) described, in 1904, the myocardial lesion which now bears his name, numerous observers, notably Coombs (4, 5), Klotz (6, 7), Swift (8) and Pappenheimer and Von Glahn (9, 10, 11) have identified similar proliferative cellular reactions in the aorta, peripheral arteries, synovial membranes of joints and tendon sheaths, cutaneous and subcutaneous nodules, pericardium, pleura, and probably in the central nervous system. From these observations it is obvious that the distribution of this granulomatous-like lesion is more extensive than was formerly believed. In the light of this knowledge, one is rather surprised to find that relatively few attempts have been made to subject the tonsils to similar microscopic studies. Virtually all who have investigated the tonsils along these lines have failed to find a lesion which could be regarded as characteristic of acute rheumatic fever Dietrich (12), Heiberg (13). In fact, MacCallum (14) has said "at least, no definite and characteristic lesion of the tonsils that would fix their position in relation to rheumatism has been described." Moreover, some

*Read before the Association of American Physicians, Atlantic City, May 4, 1927. From the departments of Medicine and Oto-Laryngology, Mercy Hospital.

years ago, one of us (15) was unable to demonstrate in the tonsil any histological picture which could be considered suggestive of rheumatic fever. As a rule those who have studied the tonsil histologically have confined their efforts largely to the tonsillar tissue proper, nor have they attempted to correlate the clinical types of rheumatic fever and the pathological findings in the extirpated tonsils, although Hambrecht and Nuzum (16) found peritonsillitis in one-third of their cases of rheumatic fever.

Stimulated by the knowledge of the wide dissemination of a distinctive lesion of rheumatic fever throughout the human body and the experimental animal; cognizant of the failure to find similar morphological responses in the lymphoid elements of the tonsil; and aware of the well-known association of tonsillitis and rheumatic fever, we undertook to examine, microscopically, the tonsils which had been removed from a series of clear-cut, unquestioned cases of acute rheumatic fever and chorea, and to correlate the clinical data of each case with the pathological processes noted in the tonsils of the same case. Furthermore, we decided to focus our attention on the capsular and periscapsular tissues of the tonsils. This decision was made for three reasons. Firstly, because previous studies by one of us, and by others, had failed to reveal convincingly characteristic lesions in the tonsillar tissue proper; secondly, because alterations in structure, especially cellular proliferative changes can be more satisfactorily observed in these regions; and thirdly, because we had observed at the time of tonsillectomy an unusual degree of peritonsillar inflammation or fibrosis in the majority of the cases of rheumatic fever and chorea. These tonsils were so adherent by virtue of the extensive inflammatory reaction that the ordinary lines of cleavage were obliterated, so that their removal was accomplished only by deliberate dissection. In those instances of recent acute rheumatic fever, following in the wake of an acute tonsillitis, the gross picture of the pericapsular tissues was that of extreme vascularity, which was out of all proportion to what one might expect from the appearance of the tonsils in situ. When the rheumatic attack antedated the operation by a longer period of time, a uniformly diffuse capsular and pericapsular fibrosis was encountered. The wide-spread distribution of this fibrous tissue was quite different from the patchy or localized deposits so frequently seen in old quinsy beds; nor was it thick and dense as the scar tissue occurring in the inveterate sufferer from peritonsillar abscesses. Whether or not the peritonsillitis was recent or old, the tonsils were always firmly fixed in their fossae.

We wish, therefore, to emphasize three features of this study. One, that all of the cases presented clear, frank manifestations of acute rheumatic fever or chorea; two, that a close correlation between the clinical findings and the pathological pictures was made in each instance; and three, especial attention was directed to the microscopic study of the capsular and pericapsular structures of the tonsils.

Our purpose in presenting this communication is to report the results of eighteen cases of acute rheumatic fever

and five cases of chorea, so studied and so observed.

The tonsils were placed in Zenker's solution immediately after their removal and blocks for microscopical sections were cut so as to include the maximum amount of the pericapsular tissues. In tonsils of a flattened character it was possible to include the capsular and pericapsular areas in one section, but in the rounded forms several sections were often necessary. In addition, one cross section of the tonsil was made in order to study its lymphoid elements. The sections were stained routinely by phloxin-methylene blue, and by hematoxylin and eosin.

Of the eighteen cases of acute rheumatic fever, thirteen were males and five were females. Their ages ranged from 12 to 52 years, five being in the second decade of life, nine in the third, three in the fourth, and one in the sixth. The average age was 26.8 years. In seven instances there was a history of previous attacks of acute rheumatic fever; of these, three had one, three had had two, and one had three previous attacks. Fourteen of the group had suffered from tonsillitis, of whom six had experienced only one attack and in eight, the tonsillitis had been recurrent. Four denied knowledge of tonsillar infection. Those individuals who had only one attack of tonsillitis said that it had occurred immediately, or very shortly, before the onset of the acute rheumatic fever. The tonsils were removed in from two days to six months following the subsidence of the rheumatic symptoms, one-half of the cases coming to operation in from two to four weeks afterwards. We considered this time interval to be safe. In all probability the tonsils could have been enucleated earlier without danger, as Morris (16) has indicated. Ten of the rheumatic cases yielded clinical evidence of valvular heart disease, which was diagnosed as mitral regurgitation in seven, mitral stenosis in two, and aortic regurgitation and mitral stenosis in one. Five individuals showed an albuminuria and one had an acute glomerulonephritis.

Five cases of chorea were similarly studied. Of these four were females, aged four, ten, twelve and fourteen years, respectively; and one was a boy of twelve. The average was 10.4 years. One of the five cases had had a previous attack of chorea and three of them gave a history of tonsillitis, one of whom had suffered from only one attack, whereas in the other two, tonsillitis had been recurrent. The tonsils were enucleated from each member of this group after the manifestations of chorea had subsided but had not disappeared. In general, a comparison of the clinical data with the pathological findings revealed that the more severely acute, and the more prolonged recurrent cases exhibited the most distinctive lesions. However, it is interesting to note that in two cases of recurrent rheumatic fever with mitral stenosis the response to the infection in the peritonsillar regions manifested itself as a very dense fibrous tissue, devoid of any mononuclear elements. One of these, a fatal case, also failed to show Aschoff nodules in the heart, but did present marked perivascular fibrosis of the coronary arterioles.

Microscopically, in the eighteen individuals with rheumatic fever, bone and cartilage, was encountered in two cases and cartilage occurred alone in three, a total of five. Fourteen of the eighteen cases showed varying degrees of perivascular infiltration, usually lymphoid and plasma cell in type. Proliferation of the endothelium of the capillaries and the perivascular lymph spaces occurred in eight cases, in five of which the character and the arrangement of the endothelial leucocytes, with multinucleate forms, suggested the granulomatous lesion described by Aschoff (3). One case showed an acute phlebitis. Bone and cartilage was found in two of the five choreic children, aged twelve and fourteen years, respectively. A lymphocytic and plasma cell infiltration occurred around the peritonsillar blood vessels in four instances. Endothelial proliferation in the capillaries and pericapsular lymph spaces was seen three times, and was shown best in one case with violent chorea, mitral stenosis and albuminuria.

The capsule of the tonsil, a fairly dense fibrous structure, blends with the pericapsular connective tissue so that the two may be regarded as one structure. The pericapsular connective tissue, of somewhat looser appearance, supports muscle bundles, adipose tissue, mucous glands, blood vessels and nerves. It is a very difficult matter to speak with certainty as to the presence of mild grades of fibrosis in this structure. As age advances, the connective tissue becomes denser which must always be considered in speaking of fibrosis in this situation. In about one-half of our cases fibrosis of the pericapsular tissues was present. In some it was very marked, so much so as to be easily recognizable at the time of the removal of the tonsils. To a certain extent the chronicity of the rheumatic fever appeared to have a direct relation to the more advanced grades of fibrosis. It may be of interest to note that fibrosis of the tonsil, itself, does not necessarily occur with pericapsular fibrosis. Where this fibrosis was marked, dense bands of fibrous tissue were found invading the numerous muscle bundles, causing the muscle fibres to be separated, compressed or often to be completely replaced by the connective tissue. The outstanding feature of the fibrous connective tissue was its collagenous character. Although loose and edematous at times, it was usually dense and compact. Curiously enough, the presence of fibroblasts was rare. We do not regard the fibrosis about the tonsil as an essential lesion of rheumatic fever, but from our material we have noted a relationship between the chronicity of the infection and the subsequent pericapsular fibrosis. Nor was it surprising to find islands of bone and cartilage in the pericapsular tissues in thirty per cent of our cases. True it is that this percentage is not much higher than that given by Weller, (18) although our own figures in a previous study (15) were much lower (3 per cent). There is nothing especially characteristic in the findings of bone and cartilage in such a high percentage in our series. It merely bespeaks a chronic inflammation and it would seem to indicate that the pericapsular tissues in rheumatic fever are involved in chronic inflammatory processes in a higher

proportion than arises from other causes.

Two changes were noted in the muscle bundles in the pericapsular tissues. Normally, the bundles are numerous and their outlines, and striations, are distinct. In some instances they were found compressed, distorted and atrophied by the invasion of the fibrous tissue. Many fibres had entirely disappeared and every gradation of change could be seen. The second alteration in the muscle was an interesting one. Associated with an active cellular infiltration of lymphoid, plasma and endothelial cells, some of the adjacent muscle fibres were split off from the main bundles by an edematous connective tissue. When these muscle cells were atrophic, they were invaded by endothelial leucocytes, forming multinucleated or giant cells. This was noted in two cases. Giant cells of muscle origin are not to be confused with the perivascular multinucleated cells of endothelial origin, to which we shall refer later. Whitman and Eastlake (19) claimed that the large multinucleated cell of the Aschoff nodule in the myocardium was of muscle-fibre origin. Their conception, however, has not been generally accepted and we believe that in the peritonsillar tissues the muscle multinucleated and the endothelial multinucleated cells can be distinguished.

Moderate thickening of the walls of the arterioles was encountered in those cases where considerable fibrosis in the pericapsular region occurred, but we would emphasize the fact that in estimating the degree of this thickening the age of the patient must be considered. There is no reason why arteriosclerosis cannot involve the tonsillar arterioles in elderly individuals. We did not find any example of excessive thickening of the arterial walls, nor any calcification of them ever seen. Fibrous thickening of the adventitial coats of the arterioles was occasionally encountered. None of the above vascular changes can be attributed solely to rheumatic fever, inasmuch as they may arise in other conditions and particularly in those individuals past middle life.

An acute and chronic phlebitis in a vessel of small size was seen in a case of severe rheumatic fever with a mitral stenosis. In the wall of the vein, the normal structures had been almost entirely replaced by the dense infiltration of lymphoid and plasma cells, and polymorphonuclear leucocytes. There was no thrombus formation, although the lumen contained erythrocytes and many polymorphonuclear leucocytes. An acute lacunar and follicular tonsillitis was present. We do not recall having seen a similar lesion in the pericapsular tissues of the tonsil, although Proskauer (20) described an acute phlebitis associated with peritonsillar abscess. No abscess, however, was found in our case.

In these sections which showed active cellular infiltration, some of the contiguous capillaries presented a well-marked endothelial proliferation. This proliferative change was also found in the lining cells of the perivascular lymph spaces. At times, these cells were large and multinucleated. Moreover, we observed a mitotic figure in a perivascular endothelial cell in a case of chorea. This endothelial reaction,

which we encountered in almost one-haf of our cases, is a definite one, and we believe, an important one. It is not possible to say that it is specific for rheumatic fever or chorea, although we have not observed this reaction in any other condition.

The mucous glands which lie at the upper pole of the tonsil have an intimate relationship to peritonsillar infection, especially quinsy, as one of us (15) pointed out some years ago. We have frequently noted lymphocytic, plasma and endothelial cell infiltration in the stroma of the mucous glands in cases where the remainder of the capsular tissue was free from inflammatory cell reaction. This observation suggests the possibility that infection may be harbored in the region of the mucous glands. The mucous glands, themselves, often presented changes indicating varying degrees of secretory activity or at other times degeneration. On three occasions there was a diffuse granulomatous reaction in the stroma about the mucous glands. In all of these, the production of large, foreign-body giant cells was a promient feature. We believe that their formation was secondary to degeneration of the mucous glands.

Discussion. Lymphoid and plasma infiltration in the capsular and pericapsular tissues of the tonsil may be caused by a variety of infections of the tonsils, as has been shown by Davis (21) and by Kellert (22). Consequently, the occurrence of this type of infiltration in three-fourths of our cases was not surprising, but it should be remembered that the degree of this infiltration varies greatly, ranging from dense, collar-like perivascular collections in some, to isolated cells, diffusely scattered throughout the stroma, in others. At times, there was little or no cellular response, save for an occasional eosinophile or tissue mast cell which occurred, as a rule, in the fibrous tissue.

The most distinctive lesion encountered in this study was a proliferation of the endothelial cells lining the smaller vascular channels and the perivascular lymph spaces. Many of these cells assumed multinucleated forms and on one occasion a mitotic figure was observed in an endothelial cell lying in the perivascular space. This finding was further evidence of endothelial activity. No demonstrable thrombus was associated with this alteration of the endothelium.

Not uncommonly, the endothelial, lymphoid and plasma cells were arranged in granulomatous structures, suggesting the Aschoff nodule. These granulomatous nodules were observed in one fourth of our cases and in none of the control cases.

Our series of control cases has not been large so that we hesitate to place this endothelial reaction, in a a category of a specific one for rheumatic fever or chorea. It is to be kept in mind, however, that controls must be very carefully selected in order to obviate the possibility of admitting an unsuspected case of rheumatic fever; as for example, it is well known that a proved mitral stenosis not infrequently occurs in the absence of a history of rheumatic fever or chorea.

Conclusions

1. In eighteen cases of rheumatic fever and five of chorea a study of the capsular and pericapsular tissues of

the tonsil showed perivascular lesions consisting of lymphoid and plasma cells, in fourteen of the former and four of the latter. In addition to this, atrophic muscle giant cells, fibrosis, bone and cartilage, and foreign-body giant cells in various parts of the tonsil were encountered.

2. An endothelial proliferative reaction of the lining cells of the capillaries and perivascular lymph spaces was noted in eleven cases.

3. Some of the endothelial cells were multinucleated and were associated with granulomatous-like lesions in six instances.

4. The endothelial cell response was the outstanding feature in this study. We are not prepared at this time to state that it is a specific reaction in the tonsil for rheumatic fever or chorea.

The authors wish to express their gratitude to Dr. S. R. Haythorn for his valuable suggestions and to Dr. H. H. Permar for his aid in the preparations of the material for microscopic study.

REFERENCES

(1) Clawson: Arch. Path. and Lab. Med., 2:799 (Dec.) 1926.
(2) Miller: J. Exper. Med., 40:543 (Oct.) 1924.
(3) Aschoff: Verhand. Deutsch. Path. Gesellsch., 8:46, 1904.
(4) Coombs: Quart. J. Med., 2:26 (Oct.) 1908-9.
(5) Idem: J. Path. and Bact., 15:490, 1911.
(6) Klotz: Tr. Assoc. Am. Physicians, 27:181, 1912.
(7) Idem: J. Path. and Bact., 18:259, 1913-14.
(8) Swift: J. Exper. Med., 39:497 (Apr.) 1924.
(9) Pappenheimer and von Glahn: J. M. Research, 44:489 (Sept.) 1924.
(10) Idem: Am. J. Path., 2:15 (Jan.) 1926.
(11) von Glahn and Pappenheimer: 235. (May) Ibid., 2:15 (Jan.) 1926.
(12) Dietrich: München. med. Wchnschr., 69:1449 (Oct. 13) 1922.
(13) Heiberg: Virchows Arch. f. Path. Anat., 257:1 (Mar. 13) 1925.
(14) MacCallum: J. A. M. A., 84:1545 (May 23) 1925.
(15) Maclachlan: "Tonsillitis, a Histopathological Study." Publications, University of Pittsburgh, 1912.
(16) Hambrecht and Nuzum: Arch. Int. Med., 29:635 (May) 1922.
(17) Morris: J. Lab. and Clin. Med., 2: 168 (Dec.) 1916.
(18) Weller: Ann. Otol. Rhinol. and Laryng., 32:687 (Sept.) 1923.
(19) Whitman and Eastlake *Arch.* Int. Med., 26:601 (Nov.) 1920.
(20) Proskauer: Med. Klin., 10: 1407, 1914.
(21) Davis: J. Infect. Dis., 10:142 (Mar.) 1912.
Idem: 10:48 (Mar.) 387 (May) 1912.
(22) Kellert: J. M. Research, 41:387 (May) 1920.

For an extensive list of references to the literature of rheumatic fever, see:

Sachs: Am. Heart, J., 1:750 (Aug.) 1926.

Uncomplicated Exudative Synovitis

(With Report of Two Cases)

By E. C. Robichaux, *M.D., Excelsior Springs, Missouri*

YOUR attention is invited to the report of two rare types of monoarticular exudative synovitis. Neither was intimately associated with acute or chronic arthritis of whatever kind, nor the immediate result of acute or chronic traumatism. One was definitely intermittent and recurrent in type, the other occurred but the one time. The etiology in both is admittedly obscure.

Case I. M. L.; aged 40; weight 220; manufacturer. Admitted October 1926 complaining of swollen knee. He was seen in three separate attacks at long intervals between. Despite the years which separated them, each attack had the main characteristics of the other. Eight years ago, he was suddenly seized with a marked swelling of the left knee entirely incapacitating him during the time of its progression. He noticed a distinct periodicity of occurrence in these attacks which progressed to a climax in two days, and then receded in two days to complete quiescence for nine days. At the end of this time it recurred, observing with each repetition, the same exacting cycle. This had continued for two years when he was first seen. Mineral waters, hydrotherapy, quinine and cacodylate of sodium were used and the condition had vanished in five weeks.

Three years later, without provocation, this condition returned. The onset was sudden. The same knee was involved. The calendar-like precision was observed of four days with and nine days without symptoms. The knee was very large but not hot. The pain was pronounced only when the joint was brought into use. It had been in progress three months when he presented himself and meanwhile, no treatment had been used. This time Liquor Potassii Arsenitis (Fowler's Solution) alone was tried and under its influence there was noticed first, a gradual delay in the appearance of symptoms and later, a diminished intensity until they had vanished altogether in five or six weeks. No other form of medication was used. Belladonna was begun but abandoned because of apparent idiosyncracy.

And now the last attack which occurred also about three years later, coming on as before without apparent physical or psychical irritation. The same knee was once more involved and showed about the same behavior as in the preceding attacks. There were no other symptoms than those found and complained of in the knee.

The family history fails to record any allergic phenomena. The personal history is unimportant except, that, he reports having had many attacks of inflammatory rheumatism and that he denies absolutely any venereal infection. His marriage is without progeny. His temperament, phlegmatic.

Examination: Tonsils out and also all devitalized teeth. Sinuses normal. Thyroid normal. The heart measures normal; there is no aortitis. There is no mitral leakage. The blood pressure is 130 over 70. The abdomen is firm and not protruding. The liver and spleen are not palpable; and no symp-

toms elicited from the gall bladder or appendix. The prostate and its adnexae are negative. The Wassermann is negative, as also the urine. Reflexes are normal. R. B. C. 5,000,000; W. B. C. 4,800; Polys. 69%; Hem. 95% (Leitz). Food allergy tests by intracutaneous method, of all foods commonly used are negative. The response to adrenalin is indefinite. Stereoscopic X-ray films in the anteroposterior and both lateral diameters made in 1923 and again in 1926 show no evidence of trophic changes at the margin of the joint surfaces. There is no destruction of articular cartilage, and no evidence of chronic thickening of the periarticular tissues.

Diagnosis: Uncomplicated Exudative Serous Synovitis or Intermittent Hydrops.

Treatment: Because the patient responded satisfactorily to the use of arsenic in the two previous attacks, neo-arsphenamine suggested itself. An immediate improvement was noticed after the first dose in that the following attack was a mere blush of others before it. There was no further trouble and a total of 5.6 grams at stated intervals completed the work.

Comment: It might be said that in intermittent hydrops, everything in medicine and surgery has been tried, including the use of blistering, bandaging, cauterizing, aspirating, injecting of substances like iodine, iodoform, carbolic acid, and finally the open operation. Of drugs, quinine, arsenic and belladonna have been the most popular. It is interesting to note that in this particular case, at least, arsenic in one form or another has proved of undoubted efficacy. I wish to emphasize the immediate result obtained with the use of arsphenamine.

The rarity of this type of exudative synovitis attracts attention. Only forty-three uncomplicated cases appear in the literature and of these only five were contributed by American authors. Dance (1) in 1831 was the first to recognize this mysterious phenomenon. He called it "Tetanos Intermittent." The report of it was made the year before his death. Perrin (2) in 1845 reports a case of the polyarticular variety occurring at night and reproducing the symptoms every seven days. Omitting all between, we find that the last report in the literature of this condition was made by MacLelland (3) of two cases in 1919.

Men and women are affected about equally. The joint most involved is the knee, although, the hip, shoulder, elbow and wrist have suffered from this peculiar malady, singly or severally. When more than one joint is involved, there is a tendency to maintain a certain regularity of alternation for the given case. In most instances the onset is sudden. The incidence is between the ages of twelve and fifty-four with an average of twenty-six years. A definite cycle is usually established for each case and varies but little during its history. The average duration of each divisional attack is three or four days, and the recurrence may continue indefinitely.

The extremes found are as follows: One case in which the symptoms lasted one hour daily and the case of Benda (4) in which the symptoms lasted eighteen to twenty-one days with an

interval of only eight days before making its appearance all over again.

There may or may not be pain, heat, redness and spasm. Subjectively, languor, headache and chilliness are common symptoms in the attack. The etiology is obscure. Osler (5) believed that it might be a manifestation of hysteria. Some have regarded it as syphilitic, others as allergic, others again as of focal origin. (6) The more popular belief is that it is a vasomotor neurosis.

Case II. T. M. C., male, aged 30, admitted March 2, 1926, complaining of severe pain and swelling in the left knee. Ten days before he attended a dinner after which several in the party had a gastro-intestinal upset. Blame was credited to a crab meat salad eaten that night. Four days after he developed a swelling of the knee, attended with much pain and fever. On examination, the knee was semi-flexed, hot and moderately distended with fluid. There was a line of redness, much as one finds in a spreading cellular infection, beginning at the inner aspect of the knee and extending roughly to a point marking the junction of the lower with the middle third of the thigh. The patient was highly neurotic. The fever was irregular, some days intermittent in character, and other days plainly remittent in type. The range of fever was 102 degrees. There was much sweating. Anorexia pronounced. Tongue coated. Heart, liver, spleen, abdomen, normal. Teeth rayed normal and tonsils out. W. B. C. 10,000, 8,000, 7,400, on March 4, 6, 11 respectively; polynuclears 72 to 62. Uric acid 1.1 mgs. to 100 c.c. of blood. Wassermann, negative and also the complement fixation test for Neisserian infection. Prostate negative. The urine contained a trace of albumin and pus, two plus, which cleared up in a few days. The serum drawn from the knee was cultured for thirty-eight hours and was negative, as also the guinea pig inoculation. Blood culture was not made. All other probable foci of infection were diligently searched for and negatived.

Treatment: Complete rest; hot packs, adrenalin in repeated doses at short intervals, salicylate of soda in large doses and iodides were useless. On the twelfth day of admittance and eighteen days after the onset of symptoms, I removed 30 cc. of fluid by needle which gave so much relief that another was done in twelve hours. No more was needed. The patient made a quick and uneventful recovery after that. He has been well ever since.

Comment: No similar case could be found in the literature. The probabilities are that this attack had its origin in the intestinal tract. Just how remains a mystery. There is no drinking to account for a possible accident at this time and no other illness of any kind prior to this development.

There is no doubt that some cases of arthritis and synovitis are the outcome of allergic sensitivity but we should then expect the articular disturbance to disappear promptly upon the omission of the offending foods. The clinical findings, plainly of infection, the long duration of symptoms, (in all twenty days) the futility of adrenalin point to some thing else than allergy. The same reasoning might apply to the theory of vasomotor neurosis. Arthritis may develop after an infection of the intestinal tract as Mutch (7) recently demonstrated in his analysis of 200 cases. Any local irritation of the intestinal mucosa might sufficiently interfere with the circulation of the blood or lymph to offer "an opportunity for infective bacteria to establish areas of infection," most often streptococcic, involving great lengths of the intestine, or it might be limited to certain cir-

cumscribed zones of greater activity from which might follow a secondary manifestation such as we have here.

Whatever the cause of this synovitis, it seemed the outcome of a sudden, transitory and aborted type of infection. In fact, the problem had apparently resolved itself very soon into one of distension sufficient to interfere with absorption.

Summary

1. A report of two cases of monoarticular exulative synovitis of obscure etiology. One is the so called "Intermittent hydrops" of which only forty-three uncomplicated cases appear in the literature. There were three main attacks of this mysterious phenomenon in six years and the interesting feature of them is, that each subdivisional attack retained, throughout, its original uncanny calendar-like cycle of progression and retrogression.

2. The efficacy of arsenical preparations is demonstrated by its successful use in each attack.

3. Record is made of the employment of arsphenamine in this case, with almost immediate result.

4. A report of an uncomplicated monoarticular exudative synovitis of undetermined etiology, with the evidence pointing to the gastro-intestinal tract.

REFERENCES

(1) Dance: Archives générales de Médecine, 1831, p. 190.

(2) Perrin, M.: Un cas curieux de contracture partielle intermittente, et épanchement de sérosite dans plusieurs articulations, J. de Med., 1845, p. 82.

(3) MacLelland, R.: Two cases of intermittent Hydrops articulorum, Lancet 1:463, 1919.

(4) Benda, T.: Intermitterende Gelenk Wassersucht. Allgem. Med. Central-Ztg. 106:483, 1900.

(5) William Osler: Principles and Practice of Medicine, Fifth Edition, p. 1118.

(6) Ely: Inflammation of Bones and Joints, Vol. I, p. 110. 1923.

(7) Mutch, N.: Arthritis and Infection of the Digestive Tract, M. J. & Rec. (Supp) 121:625. 1925.

Keen's Surgery: p. 301.

Turnbull, J. A.: Food Allergens in connection with arthritis. Boston, M. & J. Surg. J. 191:438. 1924.

Editorial

THE POSSIBILITIES OF DANGER IN THE USE OF ULTRAVIOLET LAMPS

If there is any one who reads this editorial whose memory goes back to the seventies of the last century he may recall perhaps some deep impression made upon his young mind by the talk of "blue glass." It was at the height of its vogue about the time of the Centennial, but was a popular fad rather than one countenanced by the regular profession. The latter looked more or less askance at the "blue light" practitioners, who flourished in the larger cities of the eastern states, and carried on thriving business, particularly with a clientele of wealthy neurotic individuals of the sanitarium or watering-place type. "Blue light" clubs were formed, sewing and missionary societies and ladies' literary clubs met in verandahs enclosed with blue glass; many people all over the country introduced panes of blue glass into their houses; and indeed no family was quite up to date if it did not possess a front hall with a fan—and side-lights of blue glass. At a later period these became red. There were many features about this blue glass craze that in the light of our recent knowledge are very interesting, and one book written upon the subject by a Bostonian much earlier in the development of the blue light cult makes entertaining reading. Before the eighties this fad had almost completely died out, only here and there individuals perpetuated the former belief in some peculiar efficacy of blue light by continuing to put blue panes of glass in their houses. At present the country is rushing into another excess concerning the use of light, ultraviolet rays; this time with a certain foundation of scientific knowledge and fact as a justification. As a result of the recent diffusion of knowledge concerning the important part played by sunlight, and particularly by the ultraviolet end of the sun's rays' spectrum upon all life, there has arisen almost over night a popular demand for artificial sunlight that has met with an all-too-eager commercial response. On every hand we hear people saying that they have purchased ultraviolet lamps and are using them with great benefit to themselves. During the present winter, which has been one unusually free from respiratory infections, it has been a frequent subject for conversation, that "since using our ultraviolet lamp, we have not had a single cold, although in previous winters, we had constant colds." Even physicians swell the chorus and tell tales of happy individual experiences of the same kind. Local electric shops are advertising so-called ultraviolet lamps at six and nine dollars per lamp. Self-treatment then with ultraviolet gen-

erators has in this way been widely spread, and is still spreading rapidly. Such generators promise fair to be as common household articles as the hot-water bag or electric pad. The propaganda for the self use of artificial sunlight is one of very great force, and the arguments irresistible. If sunlight is necessary to human health and happiness, when for several winter months of gloom, chill and depression, the sun is exerting its influence in the southern hemisphere and we are languishing in its absence, if artificial sunlight is possible and obtainable, it surely is folly not to make use of it. There could be no more unanswerable argument. So artificial ultraviolet light is being utilized daily in home, office and elsewhere to help those who can afford its use to get through the winter. Many of the athletic clubs and bathing establishments, particularly those connected with sanatariums, have seized upon the ultraviolet generator as an important adjunct to their paraphernalia. Nude men and women spend an hour or more daily exposed to light of unknown quality and uncertain power. There is no physician's control of such exposures, and the important thing is that light may be dangerous as well as beneficial and necessary to the normal metabolic processes of the animal body. There is, moreover, such a thing as too much light, as well as too little light. There is such a thing as too much sunlight, as sun-burn, various skin and eye affections, and unpleasant "light reactions" show. Many cases of tuberculosis are definitely harmed by light treatments and exposure of the nude body to sunlight. The useful and good facts that we do know about the action of light are extremely vital, but it is just as vitally important to know the limits of the favorable action of light and to recognize its dangers. Experimentation has shown that there is a possible optimum of favorable action beyond which it is dangerous to go. Over-exposure to ultraviolet rays reduces the lymphocytes of the blood, and in this way may possibly lower resistance instead of increasing it. Damage to certain tissues or groups of cells may result from over-exposure to ultraviolet rays; the retina, the germ-cells and the melanophores of the skin may be damaged or even destroyed. Ultraviolet light is a dangerous force, and if actinic generators are used exceeding the spectrum of the sun's rays then there are grave possibilities of danger. This danger might in part be averted by laws passed limiting the spectrum of artificial generators to that of the ordinary sun's rays. Even then indiscriminate use and overuse of the sun's rays may not be advisable, and the advice of a good physician should be given whenever the use of artificial generators is contemplated. It must be borne in mind, however, that the average practitioner is as ignorant of the harmful action of light as the average layman. This lack of knowledge is, however, being supplied by literature upon the subject furnished by the American Medical Association. Its Council on Physical Therapy has made the following report, published over a year ago in the Journal. Since that time the public exploitation of

ultraviolet generators has tremendously increased, and it is important that both physicians and laymen be again warned as to the possibilities of danger attending the sale of ultraviolet generators directly to the public and their use by the layman without medical advice.

"The Council on Physical Therapy of the American Medical Association, on the basis of the present available evidence, is convinced that the sale of generators of ultraviolet energy to the public for self-treatment is without jurisdiction. The Council bases its condemnation on the sale of such apparatus for this purpose on the following grounds:

"1. The uninformed public could not take the proper precautions in administering treatments and, as a result, severe general burns or grave injury to the eyes might ensue.

"2. Those not familiar with the possibilities of such apparatus would be led to place unwarranted confidence in the therapeutic value of such treatment by the claims that might be made in the literature advertising such generators, and to undertake to treat serious conditions not amenable to such treatment.

"3. The unrestricted possession of such therapeutic means would tend to deprive people of expert diagnosis by encouraging them to make self-diagnosis.

"4. Such practice would encourage the sale of useless and fraudulent lamps which would be advertised as generators of ultraviolet rays, since the public would have no means at its disposal to determine the quality or quantity of the radiant energy emitted by such lamps.

"For the foregoing reasons, the Council on Physical Therapy considers as detrimental to public welfare the sale or the advertising for sale, directly to the public, of a generator of ultraviolet energy. Under rule 11 of its Official Rules, the Council will declare inadmissible for inclusion in its list of accepted devices for physical therapy apparatus manufactured by a firm whose policy is in this matter detrimental to public welfare."

Dr. Julius Bauer

Dr. Julius Bauer is about 40 years of age, and is Privatdozent in Internal Medicine, University of Vienna, and a physician-in-chief to the Polyclinic located on Mariannengasse. He has a clinic on Endocrinology, which he holds at the Polyclinic on Mondays and Fridays at 5 o'clock. This is exceedingly interesting and instructive and is attended by many Americans. His chief publications are as follows: Lectures on the General Constitution and Inheritance for Students and Physicians. Second edition 1923. With Dr. Conrad Steins in 1926 there appeared a monograph on "Constitutional Pathology as illustrated by Otology." In 1917, his greatest contribution, a large volume on "The Constitutional Disposition to Internal Diseases," appeared; a second edition in 1921. This is a monumental work of 794 pages. In 1927 his latest work on Internal Secretions appeared.

Bauer is a very interesting personality; he visited America in 1925 and lectured in the East, chiefly at Buffalo. He speaks English fluently and is a splendid lecturer. He has an encyclopedic type of mind and is a persistent student. The College of Physicians is very fortunate in having his acceptance. His great contribution is his idea of Constitutional Pathology acting through inheritance, and influencing the endocrine glands, as opposed to the other conception that the endocrine glands in the individual are without influence of family or inheritance and only determined by the character of the individual make-up. Dr. Bauer has also made important contributions to the theory of cancer inheritance. His appreciation of the importance of constitutional pathology and the inheritance of disease make him at the present moment one of the leading minds in the medical philosophy of our times.

Abstracts

Respiratory Anaphylaxis, Sensitization, Shock, Bronchial Asthma and Death in the Guinea-pig by the Nasal Inhalation of Dry Horse Dander. By BRET RATNER, HOLMES C. JACKSON and HELEN LEE GRUEHL (American Journal of Diseases of Children, July, 1927).

Some years ago Ratner studied a group of children suffering from bronchial asthma, the cause of which was traced to rabbit hair. In none of these cases was it possible to obtain any hereditary evidence of protein sensitivity; the opinion was therefore expressed that the sensitization had been acquired through the inhalation of dry dust resulting from the rabbit hair present in pillows, clothing, toys and other articles. In order to prove this hypothesis it was felt necessary to produce in an animal a state of protein sensitivity through the direct inhalation of a dry animal emanation, and, further, to reproduce the symptom-complex of bronchial asthma. Sewall had already in 1914-16 shown that animals could be sensitized by nasal instillation of horse serum; and that on further treatment with horse serum, the animals developed symptoms of bronchial asthma. The oral route was found to be ineffective. In 1917, Sewall announced that he had produced all the features of bronchial asthma in the guinea-pig, and that the origin of this asthma is anaphylactic. He believed that this was not a local hypersensitiveness, but is of general nature. The present research carried out by Ratner and associates came to the following conclusions. Horse dander when used in the dry state or in solution, can serve as an anaphylactogen. The authors present a method for the preparation of dry dander, and for the extraction of an anaphylactogen from this substance. Guinea-pigs have been successfully sensitized by the inhalation of dry horse dander. Shock has been induced by the inhalation of dry horse dander in guinea-pigs previously sensitized by the injection of dander extract, and they have even been killed by it. Guinea-pigs, sensitized by the inhalation of dry horse dander, when again subjected to the inhalation of dry horse dander after a suitable incubation period showed respiratory symptoms of anaphylaxsis. The symptoms noted in the last group are not different from those observed in the human being with asthma. Epinephrine alleviates the symptoms in the latter group in the same manner in which epinephrine affects human beings suffering from an attack of asthma. The nasal route can, if conditions are proper, serve as a portal of entry for foreign proteins, in the dry or liquid state, in the same way that a parenteral injection can do so. The authors believe that foreign proteins may enter the circulation from the nasopharynx; this is based on the fact that death occurred after nasal inhalation almost as soon as after an intravenous injection. The swallowing of dry dander in capsules does not sensitize animals. A state of anaphylaxis was produced in the guinea-pig under conditions that would be regarded as natural, i.e., without the introduction of a substance by direct injection, and therefore supports the theory of "acquired" sensitization in the human being. The experimental data in the animal and clinical evidence in the human being are shown to be so closely related as to suggest the point of view that anaphylaxis in the animal and asthma in the human subject are fundamentally the same. This particular type of anaphylaxis in the guinea-pig induced by the inhalation of a dry animal emanation the authors wish to call "respiratory anaphylaxis" as opposed to anaphylaxis induced by parenteral injections. They believe that the hypothesis of Sewall, that the symptoms produced in

guinea-pigs by the intranasal instillation of horse serum have the essential character of bronchial asthma. They agree also with Sewall and Powell, 1916, that the oral administration of dry horse dander does not play any rôle in this particular type of "respiratory anaphylaxis." Whether asthma, in all instances is an acquired disease, or whether it is hereditary, cannot be answered in finality with the evidence at hand. That a certain predisposition is essential, must be accepted both for animals and human beings. What we are mainly concerned with, however, is that, given a predisposition, one can, by governed factors acquire bronchial asthma or "respiratory anaphylaxis." The authors believe that the evidence presented by them in this investigation strongly emphasizes the theory that the problem of idiosyncrasy or allergy in the human subject and that of anaphylaxis in the animal are closely related.

Note on Urine Preservatives. By J. J. Short and A. Piatetzky (Journal of Laboratory and Clinical Medicine, August, 1927).

An ideal urine preservative should have the following properties. It should preserve the urine from bacterial decomposition and the development of moulds or other growths for considerable periods of time under average conditions. It should not interfere either positively or negatively with any of the physical, chemical or microscopic tests in ordinary use. It should be readily soluble. It should not interfere to any marked extent with the normal action of the urine. It should be a solid, and its cost should be reasonable. Since 1925 the authors have tried out a large number of preservatives, such as boric acid, borax, toluene, thymol, resorcinol, salicylic acid, sodium benzoate, urofix, nitro-benzene, dinitrobenzene, nitrophenol, and various other aromatic nitro-compounds, benzoic acid, sodium bisulphate, chinosol and hexamethylamine. The last named they found to be the most satisfactory. For the preservation of 30 cc. specimens they use two compressed tablets, one of 100 mg. hexamethylamine and another such tablet containing 50 mg. each of acetyl-salicylic acid and potassium nitrate, the latter an inert substance used merely for the purpose of facilitating the feeding of the acetyl-salicylic acid into the compressing machine. The tablets are added simultaneously, and go into solution readily. The cost is extremely low as compared to that of the various urine preservatives now on the market.

The Relation Between Physique and Performance. By George J. Mohr *and* Ralph H. Gundlach (Journal of Experimental Psychology, Vol. X, April, 1927).

During recent years there have been numerous studies of the insane centering about the relationship of bodily habitus to mental disturbance. Kretschmer and other investigators have undertaken to show that there is a marked correspondence between the various forms of physical development and mental disturbance. He specifically contends that the pyknic habitus is characteristically associated with manicdepressive psychosis, while the athletic and asthenic types of habitus are clearly associated with the schizophrenic forms of insanity. Not only does a correspondence of physical build and psychic structure hold true in the field of the abnormal, but a similar correspondence may also be determined among normal individuals. Kretschmer's studies led him to believe that at least two temperamental types may be determined among the normal population and that these two types are related in character to the two major types of insanity. While the manic-depressive insanity is typically characterized by a cyclic variation in mood so that the patient may pass from a state of extreme depression to one of maniacal excitation, among the normal there are many individuals who show the same tendency, although the fluctuations remain in much narrower limits. These individuals Kretschmer considers as of the cyclothymic disposition or temperament. In contrast is that large group who evince in minor degree the characteristics that under pathological conditions become the symptoms of

the schizophrenic disorders. The well-developed symptoms of schizophrenia, such as emotional blunting, disorders of attention and disturbances in the associative processes, may find their correlatives in diffidence, pre-occupation and self-centeredness of certain normal individuals. According to Kretschmer, these are of the schizothymic temperament. Kretschmer further holds that the correspondence of certain types of physique associated with these temperaments, noted among insane patients, may also be demonstrated among the normal. He describes the asthenic, athletic and dysplastic bodily forms. The asthenic individual, said to be of the schizothymic temperament, is one who is of average height but is relatively tall for his weight. He is thin with a long narrow shallow chest. His shoulders are relatively broad contrasted with the diameter of his chest. His muscles are thin and poorly developed. The skin is thin and loosely attached to the underlying tissues. The face is characteristically long and narrow, with a prominent nose and clear-cut features. The facial angle is sharp and the mid-face is relatively long. The athletic type is similar to the asthenic in general bodily proportions, but all of the structures are thicker, firmer and of more robust development. The shoulders are heavy, the chest is broad and of medium depth. The skeleton is heavily built. The muscles are thick and closely adherent. The face is relatively long and narrow, with proportions similar to the asthenic, but with thick though well-defined features. The skin is thick and closely adherent. The face is relatively long and narrow, with proportions similar to the asthenic, but with thick though well-defined features. The facial angle is less marked than in the asthenic and the lower jaw more heavily developed. The athletic type is considered a variant of the asthenic, and is associated with the schizothymic group. The pyknic habitus is described as one in which there is an increase in the volume of all of the body cavities. The head is large, the chest is voluminous and exceptionally broad and deep. Although the shoulders are of moderate width they appear narrow in contrast with the broad chest. The abdomen is full. The skeletal structure is slight when compared with the general bulk of the individual, and the extremities are relatively small and slender. The hands are small and delicate. There is a generous adiposity, and the skin is thick and firm. The face is round and ruddy and the mid-face is short. This bodily form is associated with the cyclothymic disposition. The dysplastic type includes many deviants from the normal. In this group are those physical forms giving evidence of endocrinal disturbance, such as the eunuchoid, hypoplastic, acromegaloid, adipogenital, etc., forms. In addition to these form-types there are mixtures of the various types, and certain forms that fail to fit into the classification. As to the occurrence of these types in the insane, Kretschmer found, on the basis of study of 260 cases, that 70.3 per cent of the schizophrenic patients present physical forms corresponding with the asthenic and athletic types, and that only 2.9 per cent of these present a pyknic habitus. Of the manic-depressive patients 84.7 per cent presented pyknic build and only 10.6 per cent the athletic-asthenic form. From these findings, together with observations on normal individuals, and from characterologic studies of families of normal psychotic subjects, Kretschmer develops his entire theory of temperament and the association of temperament with physical build. Many investigators have endeavoured to determine whether the physical types can be readily identified, and further, to clarify the possible relationship of these physical forms to the insanities. Apparently, there has been little difficulty in the identification of the actual types, but there has been a wide divergence among the investigators as to the incidence of these types among the insane. There is a general agreement that there is a greater incidence of the pyknic build in the manic-depressive group, but there are also reports of typical cases of manic-depressive insanity not associated with the pyknic habitus. Mohr and Gundlach made a study of 89 native white men taken from a large prison population. Of these men 18 were of the asthenic type, 26

of the athletic type and 44 of the pyknic type, conforming to the distinguishing characters and physical measurements for Kretschmer's types. Their conclusions were as follows. The incidence of the physical types among the prison group is not markedly different from that observed by a number of investigators among the schizophrenic patients and that by Gruble among normal individuals. It is similar to that observed by von Rohden among convicts, although the incidence of pyknic forms among the Joliet group is somewhat larger. It is possible that only the lower grades of pyknic men are represented in the convicts. The physical types as Kretschmer describes them cannot be precisely differentiated by mere inspection. There is a continuous progression from the characteristics of the extreme asthenic and those that determine the "best" pyknic habitus. Grouping of the asthenic and athletic men under a single leptosome does not seem to be justified. Whatever the exact significance of the physical types may be, there is no doubt that the differences of performance of these groups can be demonstrated. Tests of "attention" and "learning" show the asthenic groups lower than the athletic subjects in three of the four tests and lower than the pyknic in the fourth. Tests based upon "inhibition" or "blocking" did not distinguish the groups. The characteristics of the cyclothymic temperament, in speed of performance, showed that in straight reaction time, speed of writing and cancellation the pyknic subjects were decidedly lower than the other groups, while the asthenic group was quite superior. The Raschach test tends to characterize the pyknic men as of a melancholic or manic disposition, while the sociological material indicates a more social life. The results support in a general way the Kretschmer theory of physical and temperamental types, in that a relationship between physique and character of performance is demonstrated. They tend to modify the theory, however, by insisting on the concept of a general progression both of performance and of physical characteristics. The asthenic subjects showed relatively more schizothymic tendencies, the pyknic subjects more cyclothymic tendencies. This bears out the evidence in the literature. The deviations in personality that constitute the symptoms of the insanities and that determine the temperaments may be conceived as ranging from extreme schizoid characteristics on the one hand to extreme manic-depressive characteristics on the other, in a manner similar to the distributions found for both performance and physical measurements. The exceptions are so numerous as seriously to impair the validity of an easily recognizable constellation of physical and psychological attributes as a type An interpretation of the facts at hand does not require the retention of the concept of "type."

Reviews

Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S. Third Edition, Thoroughly Revised. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia, Fellow of the Royal College of Physicians, London; Formerly Associate Professor of Medicine, The Johns Hopkins University. Assisted by Elmer H. Funk, Assistant Professor of Medicine, Jefferson Medical College, Philadelphia. Volume V. Diseases of the Blood—Diseases of the Lymphatic System—Diseases of the Ductless Glands—Diseases of the Urinary System—Vasomotor and Trophic Disorders—Diseases of the Locomotor System. 948 pages, 82 illustrations. Lea and Febiger, Philadelphia, 1927. Price in cloth, $9.00.

The contributors to this volume include Thomas Brown, Richard Cabot, George Dock, Charles P. Emerson, Sir A. E. Garrod, Harold W. Jones, Edmund B. Krumbhaar, H. Lisser, W. T. Longcope, John McCrae, Thomas McCrae, Archibald Malloch, J. P. O'Hare, Sir William Osler, J. H. Pratt, L. G. Rowntree, W. R. Steiner, A. S. Warthin and H. H. Young. Chapters I and II on The General Pathology of the Blood-forming Organs and Pernicious and Secondary Anemia, Chlorosis and Leukemia are by R. C. Cabot. These articles have not been brought up to date, particularly the two on pernicious anemia and leukemia. The author does not seem aware of much new thought concerning these diseases. The importance of the constitutional factor in pernicious anemia as emphasized by Faber and many others is not mentioned; the discussion of the etiology is inadequate, and there surely should have been time to incorporate into the proof-sheets a fuller discussion of the dietetic treatment of this disease. As this article stands its paragraphs on treatment are practically useless to the practitioner who will consult this new volume for recent information concerning pernicious anemia. Likewise, the section on Polycythemia is not up to date. The relationship of polycythemia to diseases of the pulmonary arteries is not considered. Ayerza's disease is not even mentioned. Pratt's articles on Purpura and Hemophilia are brought up to date and are very complete and well written. Krumbhaar's section on Diseases of the Spleen is also written with a knowledge of the recent literature, and is adequate. The same thing may be said of Jones' chapter of Blood Transfusion. Chapter VI, on Diseases of the Lymphatic Glands has been brought up to date. A typographical error on page 222 reads reticulocytosma for reticulocytoma. In Chapter VII Longcope presents the infective granuloma view of Hodgkin's disease without committment to any known etiology. His entire article is written from this standpoint, and he is apparently unfamiliar with the transitional forms between aleukemic and leukemic lymphocytomas and Hodgkin's, and the "reticulocytomas" or "reticulocytosarcomas." George Dock and H. Lisser have written the chapters on the Ductless Glands, Adrenals, Pituitary Body, Pineal Gland, Thyroid and Parathyroids. These articles are complete and well brought up to date. The same may be said of the chapter on Diseases of the Thymus by Warthin. The various divisions of Part IV, Diseases of the Urinary System have been largly revised by Roundtree, Thomas McCrae, James P. O'Hare, Thomas R. Brown and Hugh Young. The first three have attempted the difficult task of revamping the older knowl-

edge of the non-purulent forms of kidney disease from the standpoint of the modern terminology of the nephroses and the nephritides and to harmonize the clinical and pathological discrepancies. This attempt is not always quite successful, but the articles are conservative and at the same time progressive, and free of the old dogmatism of clinical and gross pathological classification, and are, therefore, very valuable treatments of this complicated subject. The more properly surgical affections of the kidneys are adequately treated from the medical standpoint. Part V, Vasomotor and Trophic Disorders, originally written by Sir William Osler, has been revised by Archibald Malloch, and presents a very complete discussion of these conditions. Part VI, Diseases of the Locomotor System, Myositis, Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, are given very adequate treatment by Walter R. Steiner. Arthritis Deformans is discussed by Thomas McCrae; Osteomalacia by Dock, and other diseases involving the skeleton are treated by C. P. Emerson. With the exception of a few instances the revision of this volume has been complete, and the majority of subjects treated are well brought up to the moment and are valuable discussions well suited to the practitioner's needs.

A Textbook of Pharmacology. By A. D. Bush, B.S., M.D., Professor of Pharmacology, Emory University, Georgia. 182 pages. P. Blakiston's Son and Co., Philadelphia, 1927. Price in cloth, $2.00.

The author says in his preface that this book on Pharmacology is written to meet the needs of the student of pharmacy and the practicing physician, since they are so busy that they cannot afford time to waste in the sifting search for essentials to which they must subject the usual textbook on Pharmacology. When a practitioner perceives the need for a medicine, he wishes to know quickly just how and where that medicine will act, what symptoms the medicine itself will produce, what symptoms it will allay and just what is the preferred method of utilizing the medicine for this particular purpose. Answers to these questions are given systematically and concisely in this book. The book is divided into three parts:—Part I, Pharmacology; II, New and Non-official Remedies; III, Prescription Writing. The general scheme is to give the name of the drug, average dose, official preparations, source, leading utility in medicine, where and how its effects are produced, usage for obtaining effect, symtoms produced by drug, symptoms it allays, leading side actions, related utilities in medicine, elimination, toxicology and contrindications. It is another handbook designed as a short and easy cut to the use of drugs in medicine, and has consequently all of the defects of the short manual. The author claims that though the student of pharmacology may later read more extensively elsewhere, he will learn elsewhere little more that is of essential value, and will return again and again to this text with the comforting assurance that here indeed is a Pharmacology that furnishes for him the very things he wishes to know. If this is true modern courses in Pharmacology in our University Medical Schools need to be revised.

Outlines of Pathology In Its Historical, Philosophical and Scientific Foundations. A Guide for Students and Practitioners of Medicine. By Horst Oertel, Strathcona Professor of Pathology, McGill University, Montreal, Canada. 479 pages. 132 illustrations including 6 colored plates. Renouf Publishing Co., Montreal, 1927. Price in cloth, $10.00.

The publisher heads his advertisement of this book with "A New View of Pathology." The author in his foreword says that "it will be apparent at once to those familiar with the subject that the scope and manner of the presentation differ in some important respects from those generally followed in textbooks. It is based on the method of teaching pathology at McGill, which deals with it primarily, not as a practical medical or premedical subject, but as a scientific and cultural branch of knowledge, and endeavors to up it in its proper setting. For this purpose the stu-

dent is introduced to it, not by taking him through its present structure, and in direct application to the art of healing, but from the standpoint of historical, philosophical and scientific orientation. In other words, he is taken to the threshold of the subject and prepared to enter it himself. To this end an effort is made to unfold critically the origin of, and trace the different methods of attack upon, the great problems in pathology, and to emphasize its constant interactions with other sciences and the theory of knowledge." The author calls his book a guide not a textbook. Another quotation is to this effect—"It seems to me much more important to open the windows of the student's mind and obtain his interest and cooperation than to burden him with nauseating thoroughness of details which change from day to day." It is evident at once that the author has a complex of pessimism directed against the modern textbook which he deplores as having been written under the influence of publishers looking for large sales, and resembling a show window in a Woolworth shop more than anything else in the world. He is determined apparently that his book should not be called practical. He believes that his book should present pathology as a science which has nothing to do with humanitarian or teleological aspects, or the relief of human ills, but solely with the determination of the lawful order and explanation of diseased life. He believes that it is much more important for the undergraduate student to obtain a clear, intelligent understanding of the general conceptions of disease, than to spend time on some one's insecure classification of streptococci, or to memorize the details of the test methods of liver function, or the various modifications in the operation for inguinal hernia, or the dosages of over a hundred pharmaceutical preparations. The first is a cultural, permanent acquisition, with which the university is principally concerned; the second are technical details of which the student himself must become master by his own, and not the instructor's volition. It is the principal purpose of the university to cultivate and refine the judgment of the students in order to fit them for an intelligent pursuit of their career. In this respect there is no distinction between "theoretical' and "practical" training for even practical application in professional careers can be based on intelligent reading. Oertel believes that pathology is at present less in need of individual efforts in discoveries and new findings than of a strictly scientific critical method. He sympathizes with the practitioner of medicine today, "drowned in a scientific mess which he is unable critically to sift." These quotations and excerpts from his Foreword are perhaps sufficient to show that this textbook on pathology is conceived in the nature of a protest against the handbook or manual type of textbook of pathology of which we have had so many published in the United States, and which present to the student only categories and catalogues of supposed scientific facts (which may be changed next year) without any unity of philosophical conception or treatment. With such a view and protest the reviewer is wholly in sympathy. Three things are necessary for a successful textbook; it should hold the known and accepted scientific knowledge of the subject; these should be held together by the fundamental philosophy of the science; and the future development of the science should be indicated whenever new lines of experimental investigation open up new paths of thought. Only when all three of these are fully taken account of can the resultant textbook be really practical and cultural. The interlarding of medical history, poetical and classical quotations, and the like, does not make of pathology a cultural course. These matters and other pertinent digressions are for the class room and the teacher, not for the textbook. The latter should be the foundation stone of the science it represents, the cultural presentation of this knowledge depends upon the teacher, his culture and his personality. While agreeing most heartily with Oertel's main thesis that pathology should be taught for its cultural value as well as for its practical (medical or hospital) application, the reviewer is convinced that this cultural value

depends upon the teacher and not upon the textbook. Classes differ, students differ, and each year's teaching, or mode of approach, must vary. Cultural teaching is a thing of the spirit, and cannot be reproduced in the black and white of a textbook; but the latter must serve as the solid foundation of fact and theory upon which the cultural should be developed by the teacher and in the student's mind itself. Culture can be given as milk or water, in overdoses, just as much as the mess of theory and facts of which Oertal so bitterly complains, but from which incubus he cannot wholly free himself. He acknowledges at the close of his foreword that "for didactic reasons" he has not entirely broken with the past, but followed it in form and contents as far as he considers compatible with this standpoint. How successful is his treatment? His contents are divided into three chapters: Chapter I, the Conception of Disease; II, Etiology and III, Pathogenesis. An epicrisis follows. The material is presented in a narrative style, at times conversational. At times this method has the advantage of catching the reader's interest, at other times a certain vagueness or looseness is produced which will leave the student in as much of a mist as the categorical presentation of facts would ever produce. Some parts are extremely good, notably the paragraphs on heredity, somatic development, parasitism and immunity. Other sections appear very incomplete, particularly the general discussion of neoplasms, the specific infections and inflammation. Disturbances of development are very inadequately treated. The protective forces of the body seem also to be incompletely considered. Etiology, except for parasitism, is too cursorily treated. The chief criticism of this book is, therefore, that of inadequacy. Nevertheless, it has great individual value. It is more refreshing and stimulating in its contrast to the average manual type of English textbook on pathology. Inadequate, when compared with the great textbooks of pathology, Aschoff and Tendeloo, this book should be recommended for collateral reading to all medical students who read in English only. We warmly advise its use for this purpose.

College News Notes

Dr. Oscar B. Hunter, F.A.C.P., of Washington, D. C., was recently elected the head of the District Medical Society there. Dr. Hunter is Professor of Bacteriology and Pathology in the George Washington University Medical School, Consulting Pathologist to the Casualty Hospital, the Montgomery County Hospital, and the Sibley Memorial Hospital, and has been active in local and national medical societies.

FOUND—Fellowship Key. Mr. John H. Dwyer, of Dwyer Bros. Lighterage, No. 4 Coenties Slip, New York, New York, has reported that on January 17, 1928, he found a watch fob with a Fellowship Key attached, on a Staten Island Ferry Boat, South Ferry, New York City. The owner can secure same by communicating with Mr. Dwyer.

"By ruling of the U. S. Commissioner of Internal Revenue, The American College of Physicians has been approved for exemption from income tax, and all amounts (Initiation Fees, Life Membership Fees and Dues) contributed to The College shall be deductible from the gross income of such donors when filing Income Tax Returns."

PAYMENT 1928 MEMBERSHIP DUES

The Executive Offices mailed to every Associate and Fellow of The College, a statement for 1928 dues on January first. A large percentage have already taken care of this obligation, and Membership Cards have been mailed to them. Others are urged to mail their checks promptly to the Executive Offices, in order that Membership Cards may be issued for admission to the New Orleans Clinical Session, and for entry on the subscription list to ANNALS OF INTERNAL MEDICINE.

OBITUARIES

Dr. Thomas H. Grosvenor, Wenatchee, Washington (Associate. April 3, 1922). Died December 11, 1927, of cerebral hemorrhage; aged 54; M.D., Northwestern University Medical School, Chicago, 1908; staff, St. Anthony's Hospital; ex-president, Chelan County Medical Society; member, Northwest Medical Society, Washington State Medical Society and Fellow of the American Medical Association.

Dr. William Henry Foreman, Indianapolis, Indiana (Associate, February 24, 1926). Aged 60 years; M.D., Central College of Physicians and Surgeons, Indianapolis, 1902; Associate Professor of Medicine, Indiana University School of Medicine.

James Campbell Todd, Boulder, Colorado (Fellow, December 30, 1921). Died January 6, 1928, following a long illness; age 53; Ph., B. Wooster College; M.D. University of Pennsylvania, School of Medicine, 1900; Postgraduate study at Harvard University Medical School; Assistant Lecturer, Associate Professor and Professor of Pathology, Denver and Gross College of Medicine, Denver, 1904-10; Professor of Pathology, University of Colorado, School of Medicine, 1910-15; Professor of Clinical Pathology, University of Colorado, School of Medicine, 1915-00; Member of Phi Gamma Delta, Phi Alpha Sigma, Phi Beta Kappa, and Sigma Xi Fraternities; Author of "Clinical Diagnosis by Laboratory Methods;" Member of local, county and state medical associations and of the American Society of Clinical Pathologists.

Meeting of

THE AMERICAN COLLEGE OF PHYSICIANS

NEW ORLEANS, MARCH 5-9, 1928

PROGRAM

Corrected and Brought Up to Present Date

MORNING SESSION, MONDAY, 10:00

Address of Welcome, Mayor Arthur O'Keefe.

Address of Welcome, President A. B. Dinwiddie, Tulane University.

Address of Welcome, Dr. J. Birney Guthrie, President, Orleans Parish Medical Society.

Address of Welcome, Dr. C. C. Bass, Dean, Tulane University School of Medicine.

1. Dr. Julius Bauer, Vienna, Austria, "Adaptation and Compensation as Origin of Disorders."

2. Dr. David P. Barr, "Multiple Myeloma."

3. Dr. L. G. Rowntree and Dr. George E. Brown, "Studies in Blood Volume with the Dye Method."

4. Dr. Joseph Sailer, "Cardiac Conditions Contraindicating the Use of Digitalis."

5. Dr. Frank R. Menne, "The Effect of Iodin on the Histopathology of the Thyroid Gland in the Instance of Hyperthyroidism."

EVENING SESSION, MONDAY, 7:45

1. Dr. Maud Sly, "Cancer and Heredity."

2. Dr. Aristides Agramonte, Havana, "Review of Research in Yellow Fever."

MORNING SESSION, TUESDAY, 10:00

1. Dr. Charles T. Stone, "The Occurrence of Severe Anemia in Myxedema."

2. Dr. W. W. Duke, "Diagnosis and Treatment of the Anemias."

3. Dr. Hilding Berglund, "Liver Diet in Pernicious Anemia."

4. Dr. C. C. Sturgis, "The Treatment of Pernicious Anemia with a Liver Fraction."

Symposium on Tuberculosis.

5. Dr. Charles L. Minor, "Modern Trends in the Treatment of Tuberculosis."

6. Dr. F. M. Pottenger, "The Cause of the Varied Clinical Manifestations in Pulmonary Tuberculosis."

7. Dr. Gerald Webb. Title to be announced.

8. Dr. Robert S. Berghoff, "Intestinal Tuberculosis."

9. Dr. John W. Flinn, "A Study of the Differential Blood Count in One Thousand Cases of Active Pulmonary Tuberculosis."

EVENING SESSION, TUESDAY—7:45

1. Dr. Allen K. Krause, "The Pathogenesis of Tuberculosis."

2. Dr. James S. McLester, "The Influence of Latent Syphilis, So-called, upon the Course of Other Diseases."

MORNING SESSION, WEDNESDAY—10:00

1. Dr. Walter M. Simpson, "Tularemia: A Clinical and Pathological Study of Fifteen Non-Fatal Cases and One Rapidly Fatal Case with Autopsy."

2. Dr. L. F. Bishop, "The Practice of Cardiology."

3. Dr. Morris H. Kahn, "Heart Strain and Its Consequences."

4. Dr. J. P. Anderson, "Discussion of the Diagnosis of Coronary Occlusion with Special Reference to Its Simulation of Acute Abdominal or Other Surgical Conditions, with Illustrative Cases."

Symposium on Epilepsy.

5. Dr. H. Rawle Geyelin, "The Relation of Chemical Influences, Including Diet and Endocrine Disturbances, to Epilepsy."

6. Dr. E. Bates Block, "The Relation of Organic Brain Disease to Epilepsy."

7. Dr. T. H. Weisenburg, "The Relation of Extra-cranial Disease to Epilepsy."

EVENING SESSION, WEDNESDAY—7:45

Symposium on Infectious Diseases.

1. Dr. C. E. Birkhaug, "Erysipelas."

2. Dr. A. R. Dochez, "Scarlet Fever."

3. Dr. Jean V. Cooke, "Specific Prophylactic Measures in Varicella and Measles."

4. Dr. J. C. Small, "Rheumatic Fever."

MORNING SESSION, THURSDAY—10:00

1. Dr. C. Saul Danzer, "The Pathogenesis and Treatment of Dyspnoea in the Light of Recent Experiments."

2. Dr. T. G. Schnabel, "A High Fat Diet in the Treatment of Migraine."

3. Dr. Henry Wald Bettmann, "Chronic Appendicitis from the the View Point of an Internist."

Symposium on Diabetes.

4. Dr. Anthony Bassler, "Chronic Pancreatic Disorders, Diabetic and Non-diabetic."

5. Dr. Frederick M. Allen, "Present Results and Outlook of Diabetic Treatment."

6. Dr. A. A. Herold, "Diabetic Therapy, with Special Reference to the Newer Remedies."

7. Dr. W. H. Olmsted, "The Dietetic Management of the Diabetic in the Doctor's Office."

MORNING SESSION, FRIDAY—10:00

1. Dr. J. L. Goforth, "Natural and Acquired Body Resistance to Neoplasia."

2. Dr. T. Z. Cason, The Progress of Medical Research in the South."

Symposium on Tropical Medicine.

3. Colonel Roger Brooke, "The Influence of the Tropics on Rickets."

4. Dr. Aldo Castellani, "Metadysentery, with Remarks on the Classification of Intestinal Bacteria."

5. Dr. Wm. M. James, "The Early Lesions of Intestinal Amebiasis."

6. Dr. Bailey K. Ashford, San Juan, Porto Rico. Title to be announced.

7. Dr. Aristides Agramonte, "Considerations upon the Etiologic Agent of Yellow Fever."

EVENING SESSION, FRIDAY—7:45

1. Dr. Julius Bauer, Vienna. Convocation Address—"Multiplicity of Factors in the Etiology of Disease."

NEW ORLEANS CLINICS.—For information as to the Clinics to be held in New Orleans, see December Annals, News Notes.

"Following the appearance of Dr. Julius Bauer, of Vienna, Austria, on the program of the Twelfth Annual Clinical Session of The College at New Orleans, March 5-9, Dr. Bauer will be available to appear before medical organizations in various parts of the United States. Dr. John H. Musser, Chairman of the Clinical Session at New Orleans (address, 1551 Canal Street, New Orleans) is arranging Dr. Bauer's itinerary, which will probably include San Diego, Los Angeles, San Francisco, Seattle, Portland, Minneapolis, Chicago, Cleveland, Philadelphia, Baltimore, and New York."

NEW ORLEANS

The City of New Orleans occupies a unique position among the large cities of the United States, because, besides being over two hundred (200) years old, one of the oldest social, medical and literary centers, the Metropolis of the South, progressive and up to date, it still retains, due to the French and Spanish influence resulting for nearly one hundred (100) years of occupancy, that subtle charm found in the cities of Southern France and Spain. This charm is felt by all those who make it their home, and during your only brief stay amongst us you will see many material evidences of it in the *Vieux Carré* (Old French Town).

But let me tell you about New Orleans, past and present in the words of some of the distinguished writers who have visited it, not only because their word pictures are better than mine could ever be, but in order to spare the modesty of a native son.

In the latter 1840's, Oakey Hall who later became Mayor of New York, speaking of the first St. Charles Hotel, which was completed early in 1837, and since destroyed by fire, exclaimed, "set the St. Charles in St. Petersburg and you would think it a Palace; in Boston (ten to one) you would christen it a College; in London and it would marvellously remind you of an Exchange; in New Orleans it is all three." Lady Wortley, an English woman who had trotted about the globe, and who wrote her

"Impressions of America," has left on record her verdict that the St. Charles was the finest piece of architecture she had seen in any place, in any part of the world. It must be remembered that this was before the United States became the hotel building, and the hotel dwelling country that it later became. In that time there was no Commodore, no Blackstone, nor even a Palmer House, or Pacific Hotel.

The following article, written by an anonymous author in Harper's Weekly of Sept. 3rd, 1859, furnishes an excellent penpicture of the Charity Hospital, built in 1832, after the earlier hospitals, the first of these erected in 1737, had been destroyed by fire.

The New Orleans Charity Hospital is one of the most celebrated institutions of its kind in the United States. Not only so, but in the liberality of its support, the commodiousness of its buildings, the systematic excellency of its therapeutic arrangements, the number of its beneficiaries, the superior skill of its attending physicians, the admirable neatness of its domestic appliances, and the impartial catholicity of its administration, it will compare favorably with the older and more renowned establishments of England and the Continent.

"Nor is it amiss to say that, whether regard be had to the ability of the Professors or the admirable advantages offered to the pupil, there is no better place in the country than New Orleans for young men who are studying to enter the medical profession."

Frederick Lewis in the October, 1927, number of the Woman's Home Companion, in an article on New Orleans says, "Amongst other things New Orleans possesses many such romantic figures of the near and distant past around whose names have gathered the anecdotes and legends which constitute the peculiar charm of the city's history. Many of them have likewise left their marks on the stones and mortar of the city's present-day structures; especially in the *Vieux Carré*, the old French quarter, where the balconied buildings which line the narrow streets recall the grandeur of other times. Here is the New Orleans that we read about in the guidebooks and the railway folders; the New Orleans which styles itself "The Paris of America"—the city of restaurants and cafés.

When it comes to New Orleans cooking I could write a book (and eat a library!). But I shall content myself with saying what I have said so many times before—in print and in person to the lovers of good food: Go to Antoine's in the French quarter. Make no resistance when the waiter brings you a tin of villainous looking baked oysters. They are a specialty of the house and remarkably good.

Go to La Louisiane. Order pompano, papillote or bouillabaisse. Go to Galatoire's. Go to a dozen other little restaurants in the back street of *Vieux Carré*. You can't get a bad meal. You may find waiting for you in the unlikeliest of places the choicest banquet of your epicurean life. Or go to Begue's where you begin to eat at eleven in the morning and keep on eating until three in the afternoon.

I can imagine that regular attendance at Begue's might prove fatal. But there are worse deaths. And New Orleans remains interesting—even in matters of interment! The places where the famous figures of New Orleans history lived during their brief period on earth are no more picturesque than the places where their ashes have lain during their long rest in the city's famous cemeteries. The old St. Louis Cemetery, where the unique practice of burying above ground was first instituted, is now closed except for the occasional admission of some long-lived and almost forgotten figure out of the city's past; but the larger and even more picturesque Matairie Cemetery is still the most ornately picturesque of New Orleans' burial grounds.

New Orleans is not behind the times. But she is content to add a few modern improvements; she isn't willing to substitute them for ancient charms. She builds beside, but not on her early glories. She still retains the brightest jewels of her crown."

So come to New Orleans for the Meeting of the American College of Physicians, you are assured a warm welcome, a splendid scientific program, and if the weather is

true to form, a mean temperature of fifty degrees, lots of sunshine and all the vegetation of spring-time.

POPULAR INTEREST IN THE CARIBBEAN CRUISE

Widespread interest has been aroused among members of The College in the post-clinical session Caribbean Cruise from New Orleans on March 10th. The United Fruit Company has advised that a considerable number of reservations have already been made, and it is anticipated that the capacity of the ship will be taken up by our members. Those who have not yet made reservations but are interested in the cruise, should complete their arrangements at once. For full description of this cruise see December Annals, College News Notes.

HOTEL ACCOMMODATIONS

New Orleans Clinical Session

The headquarters hotel for the Twelfth Annual Clinical Session at New Orleans, Roosevelt Hotel, reports that their supply of single rooms for the Clinical Session is practically exhausted from the large number of applications for reservations. There are still available double rooms at this hotel. It should be noted, however, that other hotels listed below offer excellent accommodations and are recommended to our members by the local New Orleans Committee on Hotels and Transportation. The Committee reports that many of these hotels are actually closer to the hospitals offering the clinics than is the headquarters hotel, the Roosevelt.

LIST OF HOTELS

(All Prices are for Rates per Day, European Plan)

Roosevelt Hotel, 123 Baronne St. (Capacity 750)
Single room with bath.....$5.00 to $ 7.00
Double room with bath.... 8.00 " 12.00

St. Charles Hotel, 211 St. Charles St. (Capacity 496)
Single room with bath.....$3.00 to $ 6.00
Double room with bath.... 5.00 " 8.00

Jung Hotel, 1500 Canal St. (Capacity 325)
Single room with bath.....$3.50 to $ 4.00
Double room with bath.... 5.00 " 6.00

Hotel Monteleon, 214 Royal St. (Capacity 600)
Single room with bath.....$3.00 to $ 4.00
Double room with bath.... 3.00 " 6.00

Hotel DeSoto, 420 Baronne St. (Capacity 400)
Single room with bath.....$4.00 to $ 5.00
Double room with bath.... 6.00 " 8.00

Bienville Hotel, Lee Circle, Capacity 300)
Single room with bath.....$4.00 to $ 6.00
Double room with bath.... 7.00 " 10.00

Lafayette Hotel, 628 St. Charles St. (Capacity 100)
Single room with bath.....$3.00 to $ 3.50
Double room with bath.... 4.00 " 6.00

La Salle Hotel, 1113 Canal St. (Capacity 100)
Single room with bath.....$3.00 to $ 3.50
Double room with bath.... 4.00 " 5.00

Hotel Louisiane, 725 Iberville St. (Capacity 38)
Single room with bath.....$2.00 to $ 3.00
Double room with bath.... 3.00 " 4.00

THE KELLOGG COMPANY

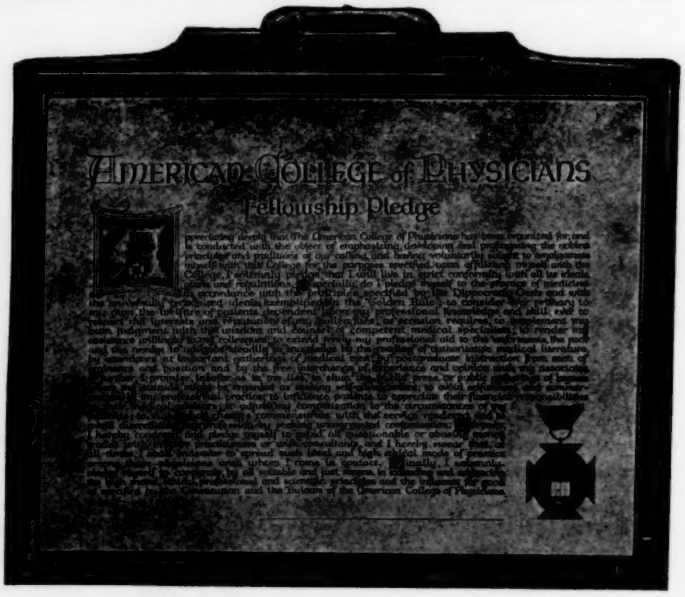
Battle Creek, Michigan

cordially invites the delegates to the New Orleans Clinical Session of The American College of Physicians to call at

BOOTH No. 36

KAFFEE HAG, the de-caffeinized coffee, and ALL-BRAN MUFFINS will be served.

The KELLOGG Booth will be in charge of a representative of their Home Economics Department, who will be glad to tell you about these two health products.



FELLOWSHIP PLEDGE
Of The
COLLEGE

—

Official Pledge and Frame

—

Price $6.00 Postpaid

Every FELLOW of The American College of Physicians should display this Pledge in his office. It is engraved on parchment, and bears the seal and colors of The College.

Send orders to E. R. LOVELAND, Executive Secretary
The American College of Physicians, 37th & Chestnut Sts.,
Philadelphia, Pa.